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Diagnosis and Management of Familial Dyslipoproteinemias

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Abstract The three major pathways of lipoprotein metabolism provide a superb paradigm to delineate systematically the familial dyslipoproteinemias. Such understanding leads to improved diagnosis and treatment of patients. In the exogenous (intestinal) pathway, defects in *LPL*, *apoC-II, APOA-V,* and *GPIHBP1* disrupt the catabolism of chylomicrons and hepatic uptake of their remnants, producing very high TG. In the endogenous (hepatic) pathway, six disorders affect the activity of the LDLR and markedly increase LDL. These include FH, FDB, ARH, PCSK9 gain-of-function mutations, sitosterolemia and loss of 7 alpha hydroxylase. Hepatic overproduction of VLDL occurs in FCHL, hyperapoB, LDL subclass pattern B, FDH and syndrome X, often due to insulin resistance and resulting in high TG, elevated small LDL particles and low HDL-C. Defects in *APOB-100* and loss-of-function mutations in *PCSK9* are associated with low LDL-C, decreased CVD and longevity. An absence of MTP leads to marked reduction in chylomicrons and VLDL, causing abetalipoproteinemia. In the reverse cholesterol pathway, deletions or nonsense mutations in apoA-I or ABCA1 transporter disrupt the formation of the nascent HDL particle. Mutations in *LCAT* disrupt esterification of cholesterol in nascent HDL by LCAT and apoA-1, and formation of spherical HDL. Mutations in either CETP or SR-B1 and familial high HDL lead to increased large HDL particles, the effect of which on CVD is not resolved. The major goal is to prevent or ameliorate the major complications of many familial dyslipoproteinemias, namely, premature CVD or pancreatitis. Dietary and drug treatment specific for each inherited disorder is reviewed.

Keywords ApoB-containing lipoproteins · ApoA-I-containing lipoproteins lipoprotein · Metabolism · Molecular defects of dyslipoproteinemia · Cardiovascular disease · Pancreatitis · Lipid-altering drugs · Familial dyslipoproteinemias

Abbreviations

CVD	Cardiovascular disease
TG	Triglycerides
CE	Cholesteryl esters
PL	Phospholipids
FC	Free (unesterified) cholesterol
VLDL	Very low density lipoproteins
LDL	Low density lipoproteins
HDL	High density lipoproteins
IDL	Intermediate density lipoproteins
CM	Chylomicrons
IBAT	Intestinal bile acid transporter
FFA	Free fatty acids
NP C-1 L-1	Niemann Pick C-1L-1
ABCG5/ ABCG8	ATP-binding cassette transporter 5 and 8
MGAT	acyl-CoA monoglycerolacyltransferase
DGAT	acyl-CoA diglycerolacyltransferase
apoB-48	Apolipoprotein B-48
apoB-100	Apolipoprotein B-100
ACAT	Acyl cholesterol acyltransferase
LPL	Lipoprotein lipase
LRP	Low density lipoprotein-like receptor protein
LDLR	Low density lipoprotein receptor
HMG-CoA reductase	Hydroxymethylglutaryl co-enzyme A reductase

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MTP	Microsomal triglyceride transport protein
apoC-I	Apolipoprotein C-I
apoC-II	Apolipoprotein C-II
apoC-III	Apolipoprotein C-III
ARH	Autosomal recessive hypercholesterolemia
SREBP	Sterol regulatory element binding protein
PCSK9	Proprotein convertase subtilisin-like kexin type 9
SCAP	SREBP cleavage activating protein
SRE	Sterol response element
SRA1	Scavenger receptor class-A1
CD36	Cluster of differentiation 36
ABCA1	ATP-binding cassette transporter 1
CETP	Cholesterol ester transfer protein
LCAT	Lecithin cholesteryl acyl transferase
HL	Hepatic lipase
PLTP	Phospholipid transfer protein
SR-BI	Scavenger receptor class B type 1
PDZK1	PDZ-domain-containing protein
BAS	Bile acid sequestrants
BA	Bile acids
GPR109A	G-protein-coupled receptor 109A
PPARα	Peroxisome proliferator activated receptor alpha
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes
FH	Familial hypercholesterolemia
LXR	Liver X receptor
GLP-1	Glucagon-like peptide-1
FDB	Familial defective apoB-100
FCHL	Familial combined hyperlipidemia
hyperapoB	Hyperapobetalipoproteinemia
USF1	Upstream stimulatory factor 1
TCF7L2	Transcription factor 7-like 2
HNF4alpha	Hepatocyte nuclear factor 4
IGT	Impaired glucose tolerance
GPIHBP1	Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
PHLA	Postheparin lipolytic activity
FHT	Familial hypertriglyceridemia
MCT	Medium-chain triglycerides
EL	Endothelial lipase
CRD	Chylomicron retention disease

Introduction

This chapter is intended to be a resource for cardiologists and other physicians and health care providers on the clinical and genetic presentation, diagnosis and treatment of disorders of hyperlipoproteinemia and hypolipoproteinemia. The major goal in adults with atherogenic familial dyslipoproteinemias is to prevent the development of premature atherosclerosis and cardiovascular disease (CVD), or the recurrence of CVD. In patients with profound abnormalities in triglyceride metabolism, the focus of treatment is to prevent pancreatitis. Those with rare disorders of hypolipoproteinemia may require treatment beyond standard dietary and drug interventions.

Overview of Plasma Lipid and Lipoprotein Metabolism

Human plasma lipoprotein metabolism is complex, but basically consists of three interrelated major pathways. These include: the exogenous (intestinal) pathway; the endogenous (hepatic) pathway and reverse cholesterol transport (Figs. 1 and 2). An understanding of normal lipid, lipoprotein and apolipoprotein metabolism is of fundamental importance to make the correct diagnosis of the dyslipoproteinemia present, to select the appropriate dietary and drug treatment, and to interpret the efficacy of treatment.

Lipoprotein Structure

The structure of plasma lipoproteins consists of hydrophobic core of triglycerides (TG) and cholesteryl esters (CE) surrounded by a hydrophilic coat consisting of amphipathic apolipoproteins, phospholipids (PL), and free (unesterified) cholesterol FC) [1, 2]. The major plasma lipoproteins are classified by their electrophoretic mobility hydrated density, or chemical composition [1, 2]. Chylomicrons, very low-density lipoproteins (VLDL), and their remnants, constitute the major carriers of TG, while low-density lipoproteins (LDL) and high-density lipoproteins (HDL) transport most of the CE.

Apolipoproteins in Lipoproteins

Apolipoproteins permit the packaging and transport of lipids and also are co-factors for enzymes and ligands for lipoprotein receptors [1, 2] (Figs. 1 and 2) (see also below). The full-length apolipoprotein B (apoB-100) is made in liver. One molecule of apoB-100 is present on VLDL, VLDL remnants, LDL, intermediate density lipoproteins (IDL) and Lp (a) lipoproteins. Apolipoprotein B-48 (apoB-48) is synthesized in intestine and is present in chylomicrons (CM) and CM remnants. ApoB-48 is the truncated product of the same gene as apolipoprotein B-100 (apoB-100), as a result of post-translational modification [1, 2]. These particles constitute the *apoB-containing lipoproteins*. Apolipoprotein A-I (apoA-I) is the major apolipoprotein of HDL and their

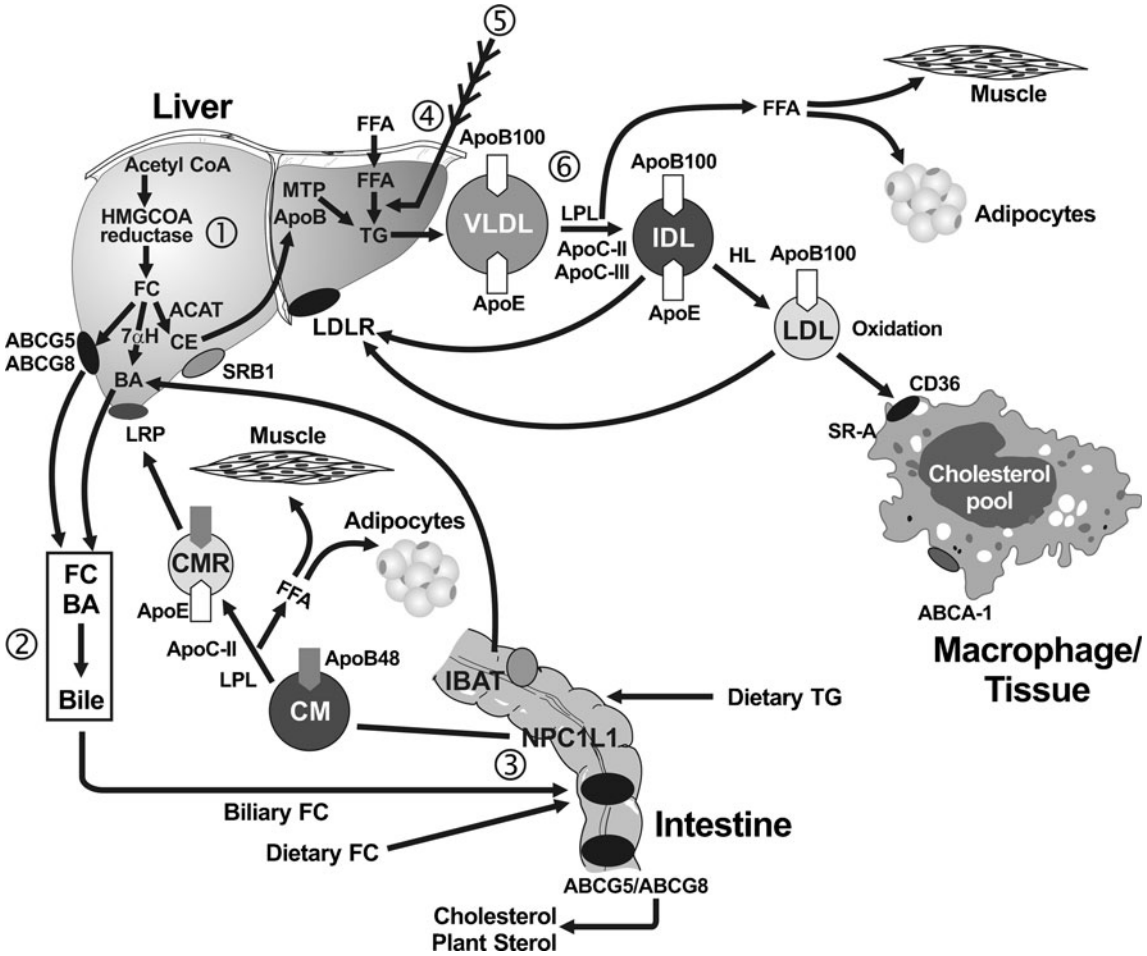

Fig. 1 Pathways of exogenous (intestinal) and endogenous (hepatic) lipoprotein metabolism. Chylomicrons (CM) transport dietary TG and cholesterol of dietary and hepatic origin. Cholesteryl esters (CE) and free cholesterol (FC) and TG are emulsified by bile acids (BA), hydrolyzed by pancreatic lipases, absorbed and re-synthesized, packaged by microsomal triglyceride transport protein (MTP) and apoB-48 into chylomicrons which are secreted. The TG in CM are hydrolyzed by lipoprotein lipase (LPL) and apoC-II producing free fatty acids (FFA), which are taken up by adipocytes or muscle. The resulting CM remnant (CMR) is then removed by the LRP receptor, delivering CE and FC to liver. BA are reabsorbed through the ileal bile acid transporter (IBAT) and recycled to the liver. FC is synthesized in the liver through HMGCoA reductase and can be excreted from the liver into bile by ABCG5/ABCG8, or converted to BA by 7 ά hydroxylase (7άH), or esterified by acyl cholesterol acyltransferase (ACAT) into CE. CE interacts with apoB-100, reducing its proteolysis, and TG is added by MCT, producing VLDL, which contains one molecule of ApoB-100 that is required for its secretion. The TG on VLDL are hydrolyzed by LPL and apoC-II, producing FFA and IDL. Some IDL is removed by the interaction of apoE with the hepatic LDL receptor (LDLR); the rest is converted into LDL by hepatic lipase (HL). ApoC-III interferes with apoE-mediated IDL uptake. LDL is normally removed by the LDLR; excess LDL can be oxidized in the vascular wall and taken up by the scavenger receptors, CD 36 and SR-A on macrophages, promoting CE storage. (With permission from: Kwiterovich, PO Lipid, Apolipoprotein, and Lipoprotein Metabolism: Implications for the Diagnosis and Treatment of Dyslipidemia. In: The Johns Hopkins Textbook of Dyslipidemia, Kwiterovich PO (Ed). Philadelphia:Wolters Kluwer/Lippincott Williams & Wilkens, 2010, pp 1–22) [1]

two major subfractions, HDL_2 and HDL_3, and is referred to as the *apoA-I-containing lipoproteins.*

Lipoprotein Metabolism of ApoB-Containing Lipoproteins: Major Receptors and Transporters

The transport of plasma lipids by apoB-containing lipoproteins encompasses both intestinal (exogenous) and hepatic (endogenous) pathways (Fig. 1).

Intestinal Lipid Transport

Absorption of Lipids. TG constitute most dietary lipid (75–150 g/d). Dietary cholesterol averages about 300 mg/day (range 100 to 600 mg/day). About 1100 mg of biliary cholesterol is secreted daily from liver into intestine (Fig. 1). In the duodenum lipids are emulsified by bile salts and hydrolyzed by pancreatic lipases. Bile acids are reabsorbed by the intestinal bile acid transporter (IBAT) in the ileum and returned to liver through the entero-hepatic

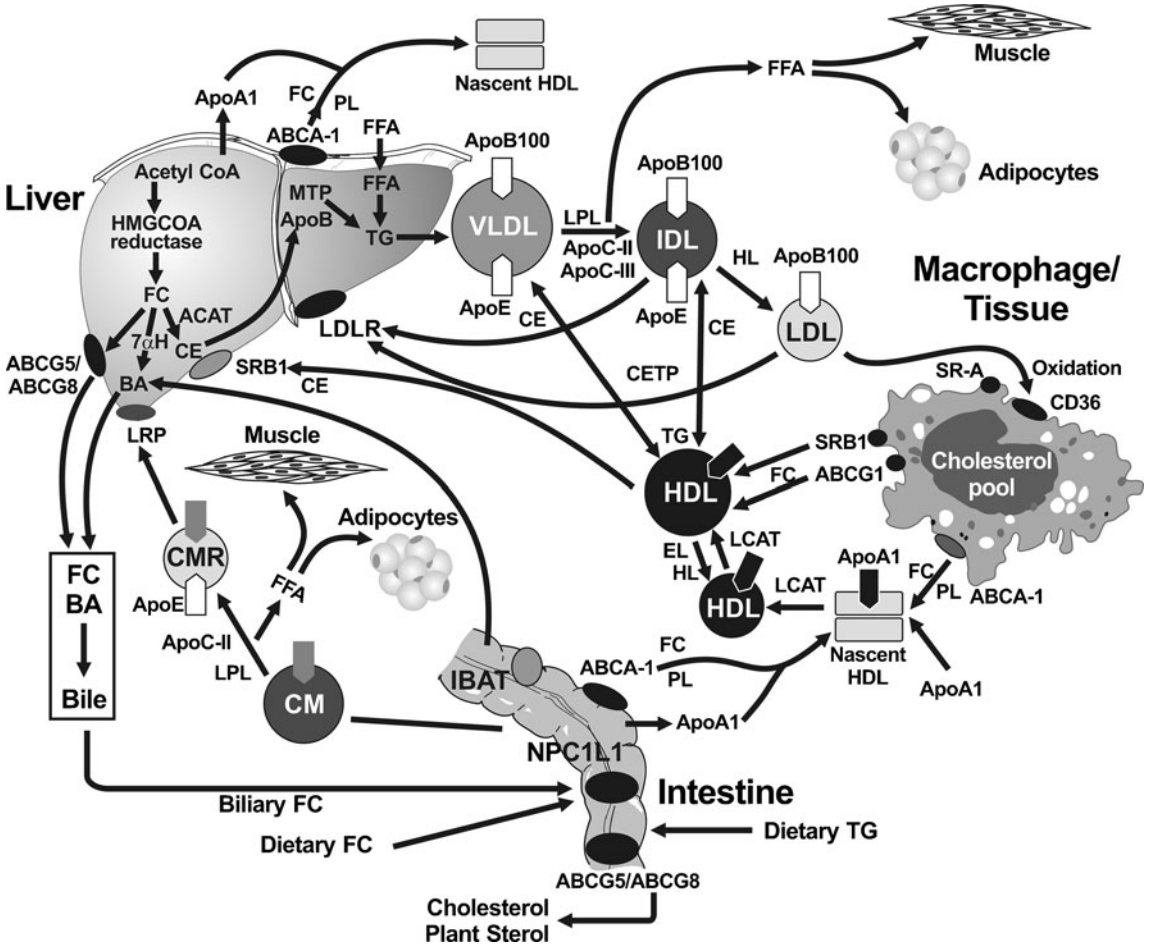

Fig. 2 The reverse cholesterol transport pathway and its interaction with the exogenous (intestinal) and endogenous (hepatic) pathways. ApoA-1 is synthesized and secreted by intestine and liver, after which it interacts with ABCA1, promoting the egress of FC and phospholipids (PL), and the formation of the nascent cigar-shaped HDL particle. Lecithin cholesterol acyl transferase (LCAT) and apoA-I catalyze the formation of CE by adding a FFA from the PL to FC, producing a spherical HDL particle, which becomes larger through LCAT activity. The large HDL exchanges some of its CE for TG from the apoB-containing lipoproteins, which are then removed by the LDLR. The CE on large HDL can also be delivered to the liver by specific uptake of the SRB-1 receptor. Once inside the liver cholesterol must be excreted into bile directly through ABCG5/ABCG8 or converted into BA by 7άH to complete the reverse cholesterol transport pathway. (With permission from: Kwiterovich, PO Lipid, Apolipoprotein, and Lipoprotein Metabolism : Implications for the Diagnosis and Treatment of Dyslipidemia. In: The Johns Hopkins Textbook of Dyslipidemia, Kwiterovich PO (Eds). Philadelphia:Wolters Kluwer/Lippincott Williams & Wilkens, 2010, pp 1–22) [1]

pathway (Fig. 1). TG are broken down into fatty acids and 2-monoglycerides, and CE hydrolyzed into free fatty acids (FFA) and FC for absorption by intestinal cells [3]. The Niemann Pick C-1L-1 (NP C-1 L-1) protein catalyzes high-affinity uptake of dietary and biliary cholesterol in jejunum (Fig. 1), about 50 % of which is absorbed daily (range 20–80 %) [4]. Two ATP-binding cassette proteins, the ABCG5/ABCG8 transporters pump excess cholesterol and plant sterols in intestinal cells back into the lumen for excretion into the stool [4] (Fig. 1).

Formation, Secretion and Metabolism of Chylomicrons. Inside the intestinal cells, FFA and monoglyceride are re-synthesized into TG through acyl-CoA monoglycerolacyltransferase (MGAT) and acyl-CoA diglycerolacyltransferase (DGAT) [3]. ApoB-48 is first lipidated by microsomal triglyceride transfer protein (MTP) and then by apolipoprotein A-IV (apoA-IV). Cholesterol is esterified by acyl cholesterol acyltransferase (ACAT). Both lipids are packaged into chylomicrons, along with apoB-48, apoA-IV and apoA-I [3], and secreted into the thoracic duct from which they enter the peripheral circulation where apoA-I and apoA-IV are exchanged for apolipoprotein C-II (apoC-II) and apolipoprotein E (apo E) from HDL.

Lipoprotein lipase (LPL) and its co-factor apoC-II, hydrolyzes TG near the endothelial lining of blood vessels [5]. FFA are taken up by muscle cells for energy utilization, or by adipose cells for re-esterification into TG (Fig. 1). Chylomicron

remnants enriched in CE and apoE are rapidly taken up by liver through sequestration by cell surface proteoglycans, followed by receptor-mediated endocytosis of remnants by apoE and the low density lipoprotein-like receptor protein (LRP) or the low density lipoprotein receptor (LDLR) [5] (Fig. 1). LRP is also called the chylomicron remnant receptor.

The uptake of dietary and biliary cholesterol is part of a process that regulates the pool of hepatic cholesterol, by downregulation of the LDLR and by inhibition of the rate-limiting enzyme of cholesterol biosynthesis, hydroxymethylglutaryl (HMG)-CoA reductase) (see also below). Hepatic cholesterol can be secreted into bile unchanged via ABCG5/ABCG8; converted by 7 alpha hydroxylase into bile acids; or, used for lipoprotein synthesis [4] (Fig. 1).

Hepatic Lipid Transport

VLDL Synthesis and Secretion. Most TG In the fasting state are carried by VLDL. The amount of apoB-100, TG and CE in liver is critical for VLDL synthesis. FFA are normally activated (fatty acid CoA) followed by oxidation, and incorporation into TG or CE [2, 6]. ApoB-100 is constitutively made in liver, i.e., regulated by proteolysis and not the expression of *APOB*. As apoB-100 interacts with CE, it assumes a new conformation, leading to decreased degradation and increased production of apoB. Microsomal TG transport protein (MTP) incorporates TG into this complex [6]. Phospholipids, apoE, apolipoprotein C-I (apoC-I), apolipoprotein C-II (apoC-II) and apolipoprotein C-III (apoC-III), are added to mature VLDL, the secretion of which requires apoB-100.

VLDL Catabolism. Hydrolysis of TG by LPL and apoC-II produces larger VLDL remnants and then smaller IDL remnants [7] (Fig. 1). IDL are relatively enriched in CE and depleted in TG. IDL are either taken up by the interaction of apoE with LDLR on liver, or hydrolyzed by HL becoming LDL, the end product of VLDL catabolism (Fig. 1).

LDL Binding and Internalization. Goldstein, Brown and colleagues [8] elegantly elucidated the LDLR pathway. After synthesis, glycosylation and transport to the cell surface, LDLR is directed to clathrin-coated pits where apoB-100 on LDL or apoE on IDL are bound with high affinity to its ligand-binding domain. (Fig. 1, central upper part). The receptor-ligand complexes inside coated vesicles are internalized by endocytosis and transported to endosomes by a modular adaptor protein, called autosomal recessive hypercholesterolemia (ARH), which is required for LDL binding and internalization but not for LDLR clustering in coated pits [9, 10] (see also below).

LDL Degradation. LDL are displaced from LDLR in the acidic environment of endosomes, permitting release of LDL into endosomes, and recycling of LDLR to the cell surface [8]. LDL are subsequently degraded in lysosomes where apoB-100 undergoes proteolysis and CE are hydrolyzed producing FC and FFA [8]. FC decreases HMG-CoA reductase and LDLR activity by inhibition of the sterol regulatory element binding protein (SREBP) pathway (see below). A protease called proprotein convertase subtilisin-like kexin type 9 (PCSK9) is secreted from liver, interacts with LDLR, and a LDLR-PCSK9 complex is internalized via clathrin-mediated endocytosis and then routed to lysosomes for degradation through an incompletely understood pathway [11, 12] (see also below).

Regulatory Effects of Intracellular Cholesterol

As intracellular cholesterol decreases, LDLR activity increases and vice versa. This regulated feedback mechanism begins with the SREBP cleavage activating protein (SCAP) that is both a sensor of sterols and an escort of SREBP [13]. When hepatocytes are depleted of cholesterol (e.g., by statins), SCAP transports SREBP from ER to Golgi, where a Site-1 protease and Site-2 protease act in sequence to release the NH2-terminal of SREBP from the membrane into the nucleus where it binds to a sterol response element (SRE) in the promoter of the LDLR and HMGCoA reductase genes, increasing their transcription [13]. Consequently, LDLR increases and LDL-C decreases. Au contraire, as hepatic cholesterol increases, SREBP cannot reach the nucleus, transcription of the LDLR and HMG-CoA reductase genes decrease, LDLR decreases and LDL-C increases [13].

Oxidation of LDL and Pathogenesis of Cholesterol Deposition. If LDL-C exceeds 100 mg/dL, the capacity to process LDL through the LDLR pathway is exceeded. Excess LDL particles that cross the endothelial barrier, are trapped in the vascular wall by proteoglycans, and modified by either oxidation or glycation [14]. Such modified LDL bind to scavenger receptor class-A (SRA1) and to CD36, a member of the scavenger receptor B family (Fig. 1), and enter cells such as macrophages by a low-affinity, LDL-receptor-independent mechanism [14] that is not subject to feedback inhibition of LDLR synthesis by LDL-derived cholesterol. LDL are taken up in an unregulated fashion, leading to excess deposition of FC and CE in macrophages (Fig. 1), the formation of foam cells, atherosclerosis and xanthomas [14].

Lipoprotein Metabolism of ApoA-I-Containing Lipoproteins: Major Receptors and Pathways

Reverse cholesterol transport refers to the process by which FC is removed from extra hepatic tissues, and ultimately transported to liver, from which it can be excreted into the intestine, either as FC or as bile acids (Fig. 2).

Synthesis of HDL

Lipidation of apoA-I and Formation of Nascent HDL. ApoA-1 is secreted as a lipid-free protein from intestine and liver. ApoA-1 interacts with the ATP-binding cassette transporter 1 (ABCA1), on the basolateral membranes of enterocytes, hepatocytes, and macrophages, attaining FC and phospholipids (PL) to form a more stable nascent HDL particle [15, 16] (Fig. 2). CE are transferred from the core of spherical HDL to TG-rich lipoproteins, a reaction catalyzed by cholesterol ester transfer protein (CETP) that exchanges CE from HDL for TG from TG-rich lipoproteins.

Formation of Larger, Mature HDL Particle. Transition of disc-shaped nascent HDL to spherical HDL requires LCAT (lecithin cholesteryl acyl transferase) and its co-factor apoA-I to catalyze the transfer of FFA from the PL, lecithin, to FC, forming CE, which constitute the neutral lipid core of spherical HDL_3. Larger HDL_2 particles are formed with further LCAT activity [15] (Fig. 2).

Transfer of Lipid Between apoA-I Containing and apoB-Containing Lipoproteins. CE are transferred from the core of spherical HDL to TG-rich lipoproteins, a reaction promoted by cholesterol ester transfer protein (CETP), which exchanges CE from HDL for TG from TG-rich lipoproteins [16] (Fig. 2). If CE-depleted, TG-enriched HDL are hydrolyzed by HL, a smaller HDL particle is produced that appears to be more avidly removed by cubulin into the kidney. PLTP, structurally similar to CETP, catalyzes the transfer of unsaturated fatty acids on PL of the apoB-containing lipoproteins to HDL, stimulating the acquisition of PL by HDL.

Reverse Cholesterol Transport

CE within spherical HDL are transported back to liver by two mechanisms: transfer by CETP from HDL to apoB-containing lipoproteins that are taken up LDLR or LRP [16] (Fig. 2); or direct delivery to liver through scavenger receptor class B type (SR-BI), also called the "HDL receptor" with help from its adapter protein, the PDZ-domain-containing protein, PDZK1 [17]. FC is excreted directly into bile, or converted into bile acids by 7 alpha hydroxylase (Fig. 1). Reverse cholesterol transport explains, at least in part, the protective effect of HDL and apoA-I against atherosclerosis and CVD but the precise HDL subclass responsible is not clarified. Conversely, factors that impede this process, such as diabetes, promote a dysfunctional HDL, appear to promote atherosclerosis.

Lipid, Lipoprotein and Apolipoprotein Levels and Their Cut Points

The plasma levels of lipids, apolipoproteins and lipoproteins are distributed over a wide range of values (Table 1). This is not unexpected given the complexity of the major pathways for lipoprotein metabolism (Figs. 1 and 2), the multiple genes and proteins involved, and the influence of other factors, such as diet, weight, gender, age, ethnicity and country. The genetic determinants affecting the plasma lipoprotein distributions have been elegantly reviewed elsewhere [2]. The distributions presented here are derived from adults in the Framingham Offspring Study where all the measurements were performed in the same subjects and by the same laboratory methods [18–21]. Distributions from other countries may vary. Those for children are considered in detail elsewhere [22].

The extremes of these distributions >95th % or <5th % (Table 1) are often used to define whether a given lipid, apolipoprotein or lipoprotein measurement is high or low. A lipoprotein phenotype is defined as the first step at identifying a patient who may have a familial disorder of lipoprotein metabolism. Values (< 95th to 75th %) and (25th to 5th %) are used to identify those with borderline elevated hyperlipoproteinemia , or borderline low hypolipoproteinemia, respectively (Table 1).

Treatment Goals

Treatment goals for LDL-C for European, Canadian and American populations are <70 mg/dL % for someone with CVD, CAD risk equivalent, diabetes or at very high risk of CV, and <100 mg/dL in someone at high risk of CVD or two risk factors for CAD. Such treatment goals based on clinical trial evidence are not available for TG and HDL-C. Thus, the definition of elevated TG and low HDL-C is arbitrary. So is any therapeutic goal. Age- and gender-specific cutpoints (Table 1) are often used as an approximation of high (>95th %), borderline high (75th to 95th %), normal (74th to 26th %), borderline low (25th to 5th %), and low (<5th %)

Metabolic Mechanisms of Treatment of Dyslipoproteinemia

Metabolic Effects of Dietary Treatment of Dyslipoproteinemia

Reduction of dietary cholesterol and saturated fats lowers LDL-C. Less dietary cholesterol is available for uptake through Niemann Pick C1 L1, leading to decreased hepatic cholesterol content (Step 3). The hepatic pool of intracellular FC decreases, which upregulates LDLR activity (see above),

Table 1 Estimated percentiles of selected plasma lipids, lipoprotein cholesterols and particles, and apoLipoproteins

Percentiles	5th	10th	25th	50th	75th	90th	95th
ApoB-contianing lipoprotein				mg/dL			
LDL-C	80	90	110	130	160	180	200
Non-HDL-C	110	120	140	160	190	210	230
ApoB	60	70	80	100	80	140	150
TG men	46	55	75	112	173	252	324
TGwomen	41	46	50	83	124	182	221
				nmol/L			
LDL-P	800	900	1100	1400	1800	2000	2010
ApoA-I containing lipoproteins				mg/dL			
HDL-C men	28	31	37	43	51	61	67
HDL-C women	35	39	46	55	66	77	84
ApoA-I men	*92*	99	114	130	153	178	106
ApoA-I women	107	116	132	159	181	206	224

Data are those from adults from the Framingham Heart Study [18–21]

LDL-C low density lipoprotein cholesterol; *non-HDL-C* non-high density lipoprotein cholesterol; *ApoB* apolipoprotein B; *TG* triglycerides; *LDL-P* total number of LDL particles; *HDL-C* high density lipoprotein cholesterol; *ApoA-I* apolipoprotein A-I

increases uptake of LDL and IDL and decreases their plasma concentrations. Saturated fats (and trans fats) have reduced affinity for ACAT (Fig. 1), decreasing CE formation and increasing FC, leading to decreased production of LDLR. Unsaturated fats increase CE, and decrease FC by stimulating ACAT, reducing the FC pool and increasing LDLR.

Other Non-pharmacologic Interventions on Dyslipoproteinemia

After dietary intervention (see above), preferably using a registered dietician, other therapies can be effective to treat dyslipoproteinemia. These include reduction to ideal body weight; decrease in simple sugar; elimination of fructose; use of regular aerobic exercise (1000 calories/week); and cessation of cigarette smoking. The latter two hygienic measures may increase HDL-C 5 to 10 mg/dL. Treatments to lower LDL include: 1.) Dietary fiber (25–30 grams/day), including 7–13 grams of soluble fiber; 2.) Plant stanols/sterols (2 grams/day); 3.) Replace animal protein with soy protein (25–50 gm/day). Two meals of fatty fish twice weekly, or capsules of OTC (omega-3 fatty acids, 1–4 gm/day, lower TG. The first three therapies may lower LDL-C about 10–30 % and fish oils may lower TG 20 to 50 %.

Metabolic and Therapeutic Effects of Pharmacologic Treatment

Agents that Affect LDLR Activity. The statins, bile acid sequestrants (BAS) and ezetimibe all produce a fall in the hepatic cholesterol pool, leading to upregulation of LDLR, and a decrease in LDL-C and IDL-C, but by different mechanisms (Fig. 1, Table 2). At Step 1, the activity of HMGCoA reductase is competitively inhibited by statins decreasing cholesterol biosynthesis, At Step 2, the reabsorption of BA through IBAT is prevented by the BAS that bind BA and transport them out in the stool. More cholesterol is converted into BA in liver by 7 alpha hydroxylase, decreasing the FC pool. At Step 3, ezetimibe inhibits absorption of dietary and biliary cholesterol by about 50 %, which decreases hepatic cholesterol (Fig. 1, Table 2).

In both Steps 2 and 3, a compensatory increase in cholesterol biosynthesis occurs that decreases the efficacy of both BAS and CAI on LDL-C reduction. When either of these two agents is combined with a statin, the statin mitigates the compensatory increase in cholesterol biosynthesis, providing a complementary decrease in LDL-C of 50–60 % [23].

Agents that Decrease TG. Niacin, fibric acid derivatives (fibrates) and omega-3-fatty acid esters can effect a significant reduction in TG [24] (Table 2).

Niacin (nicotinic acid) reduces the synthesis of TG and VLDL (and consequently LDL). The current hypothesis is that niacin inhibits hydrolysis of TG by hormone sensitive lipase in adipocytes through its G-protein-coupled receptor 109A (GPR109A), leading to decreased FFA mobilization to the liver and reduced production of TG [24, 25]. This hypothesis has recently come under question. In mice, the absence of GPR109A had no effect on niacin's lipid efficacy despite complete abrogation of the anti-lipolytic effect. In three human trials, two novel, full GPR109A agonists, MK-1903 and SCH90027, lowered FFAs acutely in humans; however, neither had the expected effects on serum lipids. Chronic FFA suppression was not sustainable agonists of GPR109A, niacin, MK-1903, or SCH900271 [26].

Fibrates. Fibrates increase hydrolysis of TG by stimulating LPL (Step 5). Fibrates are agonists for the nuclear receptor peroxisome proliferator activated receptor alpha (PPARά) in liver, which increases *LPL* but decreases a*poC-III* (an

Table 2 Metabolic, therapeutic and adverse side effect in lipid altering drugs

Drug class	Drugs available	Dose range*	Mechanism of action	LDL-C reduction	TG reduction	HDL-C increase	Side effects	Drug interactions
Statins	Atorvastatin Fluvastatin Lovastatin Pravastatin Simvastatin Rosuvastatin	10–80 mg/day 20–80 mg/day 20–80 mg/day 10–80 mg/day 10–80 mg/day 5–40 mg/day	Inhibition of HMGCoA reductase Upregulate LDLR Decrease LDL and IDL Lower TG; increase HDL-C	30.50 % 20–30 % 20–40 % 20–40 % 25–50 % 30–60 %	10–40 %	3–15 %	Muscle pain, tenderness, weakness rhabdomyolysis; increased LFTs; GI complaints; headache; joint pain, memory loss (?); weakness; tiredness; loss of taste, increases anticoagulents	**Drugs metabolized by hepatic cytochrome P450 enzyme 3A4 increases levels of atovastatin, lovastatin and simvastatin increase risk of rhabdomyolysis
BAs	Chlolesyramine Colestipol Colesevelam	4–24 g/day 3 to 6 tablets of 625 mg each/day	Sequester BA for excretion into stool Upregulate LDLR Decrease LDL	10–20 %	Variable	3–5 %	Constipation, abdomen pain, vomiting, bloating, diarrhea, heart burn, gall stones	The BAS, cholystramine, can decrease the absorption of a number of vitamins and drugs:# Colesevalam suitable alternative
CAI	Ezetimibe	10 mg/day	Inhibit FC absorption Upregulate LDLR Decrease LDL	15–20 %	5–20 %	3–5 %	Headache, dizziness, diarrhea, joint pain, myalgias, tiredness, swelling. rash	Increased LFTs with statins ezetimibe with cyclosporine increases the blood levels of each.
Niacin	Crystalline niacin Extended release niacin Sustained release niacin	1000–3000 mg/day 1000–2000 mg/day 600 to 1200 mg/day	Inhibit FFA mobilization and decrease production of TG, VLDL and LDL; Decrease HDL degradation	15–20 %	20–50 %	15–35 %	Itching, rash, burning of skin and redness, gastritis, elevated LFTs; uric acid and blood sugar, diabetes, bloating, nausea, diarrhea, dizziness, faintness, rapid heart beat (arrhythmia) elevated LFTs and jaundice, acanthocis nigracans	Increased LFTs with statins
Fibrates	Fenofibrate (Artara) (Loibra) (Tricor) (Trilipix) Gemfibrozil	43=139 mg/day 67–200 mg/day 48–145 mg/day 45–135 mg/day 600–1200 mg/day	Stimulate LPL & inhibit APOC-III Decrease TG Increase HDL production Decrease small LDL particles Increase small HDL particles	5–20 % (may increase LDL = C in some hyperTG patients)	25–50 %	6–15 %	Headache, dizziness, diarrhea, back and joint paint; increases prothrombin time; gall bladder stones; increases creatinine (fenofibrate).	Gemfibrozil can interact with any statin, particularly the four that undergo glucuronication, increasing the chance of myositis and rhabdomyolysis; fenofibrate is a suitable alternative
Omega-3 fatty acid Esters	EPA DHA	1 to 4 g/day	Decrease TG and VLDL production by inhibiting FFA and TG biosynthesis	−1 % 3 %	25–50 %	1 % 7 %	Burping, heart burn, nausea, change in taste, back pain, rash	Allergy to fish or shellfish; anticoagulants; beta blockers and diuretics (hypotension)

*The comparative efficacy of the individual statins (mg/day) is: rosuvastatin 5 mg: atorvastatin 10 mg; simvastatin 20 mg; lovastatin and pravastation 40 mg; fluvastatin 80 mg. A decrease in LDL-C of 30-40 % can usually be achieved at these dosages. A reduction of IDL and TG ages

**azole antifungals, macrolide antibiotics, protease inhibitors, amiodarone, calcium channel blockers (diltiazem, verapamil) antidepressents such as sertraline, nonsedating antihistamines, cyclosoirine, and grapefuit juice

folic acid, vitamins A, D and K and anionic drugs, including digoxin, warfarin, thyoxine and thiazide diuretics. Colesevalam does not have these interactions

inhibitor of LPL) expression, both promoting TG hydrolysis, and improving apoE-mediated uptake of TG-rich remnants by liver and reducing TG [24] (Fig. 1, Table 2). The statins may decrease production of TG and VLDL in liver leading to decreased TG [24].

Omega-3-fatty Acid Esters. These agents are derived from fish oils and are believed to reduce TG and VLDL synthesis and to increase VLDL catabolism, leading to a significant reduction in TG [24] (Step 6) (Table 2). Omega-3-fatty acids appear to impair the production of FFA by deceasing the enzymatic conversion of acetyl CoA into FFA and increasing the oxidation of FFA.

Agents that Increase HDL-C. Each of the lipid altering drugs increases HDL-C (Table 2), with niacin being the most effective, the fibrates second, and the statins third [27, 28]. Niacin decreases the catabolism of apoA-I, while the fibrates and statins increase apoA-I production [27] (Fig. 2).

Effect of Lipid-altering Drugs on Coronary Artery Disease, Their Side Effects and Drug Interactions

Statins. The statins produce a significant fall in LDL-C (Table 2) and are the drugs of choice for primary and secondary prevention of CAD [28]. The side effects of the statins [29] are summarized in Table 2. While well tolerated in most patients, myalgia and myositis occurs in a higher proportion of patients than indicated in the statin trials. Lower doses of statins and co-enzyme Q (100–200 mg per day) may help muscular symptoms. Agents that increase blood statin levels should be discontinued (Table 2). Statins should be discontinued if the CK level is >500 with muscle symptoms or >1000 without symptoms. Rhabdomyolysis occurs in <0.5 % of patients; this potentially life threatening complication is dose related and reaches 0.8 % on simvastatin at higher doses (Table 2) [29]. Combination regimens with statin, niacin, and intestinally active LDL-lowering drugs are useful alternatives to high-dose statin therapy [30].

There is no substantial evidence that the statins cause cognitive decline or cancer, although there is a small but significant increase in type II diabetes in the statin trials [31]. Statin therapy is an effective intervention in the secondary prevention of CVD in both sexes, but there is no benefit on stroke and all-cause mortality in women [32].

BAS and Ezetimibe. The BAS and ezetimibe both produce a reduction in LDL-C of about 15 to 20 %; the BAS decrease CAD [28, 30]. Ezetimibe in combination with simvastatin, compared to simvastatin plus placebo, has been shown to safely reduce CAD in patients with chronic kidney disease. The intestinal side effects of BAS, namely, their interference with absorption of vitamins and anionic drugs, does not occur with the second-generation agent, colesevelam (Table 2). Side effects of ezetimibe are relatively minor (Table 2). Ezetimibe and cyclosporine can increase the blood levels of each other. The combination of ezetimibe with BAS (especially colesevelam) had a significant effect on the lipoprotein profile in hyperlipidemic patients but their combined effect on CAD is not known [33].

Niacin. Niacin has been used for over 50 years and was shown to decrease CVD [25]. It has potentially useful properties – it increases HDL-C by 15–30 % with an associated increase in Apo A1 and also lowers TG (up to 35 %), LDL-C (about 20 %) and lipoprotein A (about 30 %), which lowers Apo B. Although favorable effects have been observed on angiographic measures and on reduction of carotid wall area quantified with MRI after 1 year of therapy, two recent clinical studies have not confirmed the usefulness of niacin for cardiovascular prevention. The recent AIM-HIGH Study showed that patients with CVD with low LDL-C levels on statin (or statin plus ezetimibe) treatment and low HDL-C at baseline randomized to Niaspan plus simvastatin versus simvastatin plus placebo did not have a significant reduction in recurrent CVD despite a significant increase in HDL-C in the Niaspan group [34, 35••]. Furthermore the HPS-2THRIVE trial (http://www.clinicaltrials.gov/ct2/show/NCT00461630?term=HPS-2THRIVE&rank=1) in which more than 23,000 patients with known vascular disease were randomized to placebo or niacin/laropiprant on a background of statin or statin/ezetimibe therapy, was stopped prematurely after a median follow up of 3.9 years as it was revealed that the active treatment did not significantly further reduce the risk of the composite end-point and there was an increase incidence of nonfatal serious side effects (http://www.mercknewsroom.com/press-release/prescription-medicine-news/merck-announces-hps2-thrive-study-tredaptive-extended-relea).

The side effects of niacin can be both annoying and potentially serious (Table 2) [25]. An extended release niacin, Niaspan (Abbott Laboratories, Abbott Park, Illinois) significantly decreases the flushing, itching and elevated LFTs seen with immediate release niacin, along with greater efficacy and safety than sustained release niacin, However, Niaspan still requires the use of aspirin or ibuprofen 30–60 minutes before the once daily dose at bedtime, along with a low fat snack. Niacin can increase FBS and rarely induce type II diabetes. Increased uric acid and occasionally gout can result from niacin use.

Fibrates. Gemfibrozil decreased CAD in men with combined dyslipidemia compared with those on placebo [28]. The side effects of fibrates are pleiotropic [36] (Table 2).

When combined with statins, gemfibrozil can be effective in treating combined dyslipidemia but this combination increases the risk of myositis and rhabdomyolysis. Fenofibrate is the suitable alternative. Fenofibrate increases the steady state levels of ezetimibe by 50 % but this is not clinically significant, and this combination can be quite effective in treating combined hyperlipidemia [36]. A paradoxical reduction in HDL-C of >30 % can occur in combined dyslipidemic patients treated with fenofibrate but it is rare [37].

Omega-3-fatty Acid Esters. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are naturally derived from fish oils and can be as efficacious as fibrates in lowering TG [24]. However, their effect on CVD remains controversial [24]. These fatty acid esters lower TG about 30 % when baseline TG is <500 mg/dL [38], and reduce TG up to 50 % when baseline TG are >500 mg/dL without serious side effects [39] (Table 2). As well, when EPA and DHA are added to statins, the combined dyslipidemias can be further improved [40].

New Lipid-altering Agents

Novel drugs are needed to improve our treatment of inherited dyslipidemias. Some potential targets to lower LDL, employing mechanisms distinct from statins include: inhibitors of MTP; antisense oligonucleotides against apoB-100 and PCSK9; and monoclonal antibodies against PCSK9. The later agents are particularly interesting; one lowers LDL-C about 50 % beyond statins in heterozygotes for familial hypercholesterolemia (FH) [41] and in statin-intolerant patients [42•]. An inhibitor of CETP, anacetrapib, essentially doubles HDL-C and lowers LDL-C and Lp (a) lipoproteins [43•]. Torcetrapib and dalcetrapib have been taken off the market, the former due in part to increased CVD events, hypertension and adrenal side effects, the latter due to no decrease in CVD events, despite being safe. Mimetic peptides of apoA-I raise HDL [44]. Others not shown in Fig. 1 include agonists for liver X receptor (LXR) and GPR109A and an antagonist for the cannabinoid receptor [44]. During the last decade, bile acids emerged as integrated regulators of metabolism via induction of various signal transduction pathways. The BAS, colesevelam, increases Glucagon-like peptide-1 (GLP-10 secretion and improved glucose levels and insulin resistance in diabetics [45, 46].

Genetic Disorders of Dyslipoproteinemia

Disorders Affecting LDL Receptor Activity

The regulation of the activity of the LDLR is critical to control the levels of atherogenic LDL. Brown and Goldstein discovered the LDLR in the process of their pioneering work on the genetic basis of FH [8]. FH is the prototype for disorders affecting the LDLR. There are actually five well-established disorders that result from mutations either in the LDLR *per se*, or from mutations in other genes that impact LDLR activity. The elevated LDL-C levels can vary considerably in these five conditions (see also below) but each disorder manifests early atherosclerosis, premature CVD, and xanthomas [10]. These disorders include: FH [10, 47], familial defective apoB-100 (FDB) [10, 48, 49]; (ARH) [10, 50, 51]; sitosterolemia [10, 52, 53] and mutations in PCSK9 [10, 12, 54]. Each disorder warrants diet and drug therapy to decrease premature atherosclerosis and CVD (see below under treatment).

Familial Hypercholesterolemia. FH is an autosomal dominant that usually presents in the heterozygous state in children [22] with levels of LDL-C that are elevated 2–3 fold above the 50th % (Table 2) [8, 10]. FH is one of the more prevalent (1 in 500) Mendelian disorders expressed in man. FH results from one of more than 900 different mutations in the LDLR gene [10]. These mutations include insertions, deletions, and missense and nonsense mutations, which can affect the normal synthesis, transport, LDL-binding ability, and clustering (in coated pits) of the LDLR [10] The impaired ability of the LDLR to function leads to decreased update of LDL from plasma and increased LDL levels (Fig. 1).

Rarely, two heterozygotes will marry (one in 250,000) and one of four children, on average, will inherit two mutant alleles for FH (one in a million) and be a FH homozygote. FH heterozygotes manifest a 2–3 fold increase in LDL-C, CVD and tendon xanthomas usually in the fourth, fifth or sixth decades. FH homozygotes have a 4–6 fold (or higher) increase in LDL-C, often develop CVD and aortic stenosis in the second and third decades, and almost always manifest planar, tuberous, and tendon xanthomas in the first decade. FH homozygotes can develop significant lesions of occult atherosclerosis in the first decade and 64 slice CT of the coronary arteries with angiography are recommended at baseline evaluation.

Phenocopies of FH Homozygotes. Planar, tendon, or tuberous xanthomas can be detected in children and adolescents presenting with one of the other four disorders affecting LDLR activity as well as adolescents with the dominant form of dysbetalipoproteinemia (see below). Those with secondary disorders of dyslipoproteinemia associated with xanthomas, such as biliary cirrhosis, congenital biliary atresia, Alagille syndrome, myelomas, and Wolman disease have other salient clinical findings that distinguish them from FH homozygotes.

Familial Defective apoB-100. FDB is an autosomal dominant that results from mutations in the gene encoding apoB-100 (such as substitution of glutamine for arginine at residue 3500), leading to a defective apoB-100, and decreased binding and clearance of LDL by LDLR from plasma [10, 48] (Fig. 1).

Heterozygotes for FDB are relatively common (e.g., 1 per 1000 in Europeans) [10]. LDL-C levels are elevated to a mild, moderate or marked degree [10, 48, 49]. The relatively smaller increases of LDL in FDB is due to a significantly decreased input rate of LDL apoB, combined with an increased clearance of LDL precursor particles via the LDL-receptor and apoE-receptors, and a decreased conversion of IDL to LDL [49]. Some patients with FDB (1 in 20) manifest a more marked form of hypercholesterolemia, similar to FH heterozygotes, and develop premature CVD and tendon xanthomas [10, 48]. FDB patients with moderate hypercholesterolemia tend not to have premature CVD [10, 30, 48].

Autosomal Recessive Hypercholesterolemia. The ARH protein normally interacts with the cytoplasmic component of the LDLR, and other cell surface oriented molecules, allowing their tyrosine phosphorylation. An adaptor protein called autosomal recessive hypercholesterolemia (ARH), after the disorder that permitted its discovery (see also below), couples the LDLR to the endocytic machinery, permitting LDLR internalization. The deficiency of the ARH protein prevents the normal internalization of the LDLR [50, 51] (Fig. 1), leading to marked elevations of LDL-C levels. ARH is a rare autosomal recessive expressed in childhood with LDL-C levels that usually range from 350 to 550 mg/dL and that can be accompanied by planar and tendon xanthomas and premature CVD [50]. ARH can be distinguished from FH homozygotes in two ways: both parents of an ARH child usually have normal lipoprotein profiles; and, an assay of LDLR function in cultured skin fibroblasts from children with ARH is usually normal or mildly decreased [51]. At least six mutations have been found in the ARH gene on chromosome 1 in Sardinian and Lebanese kindreds [51].

Sitosterolemia. Sitosterolemia (also called phytosterolemia) is a rare autosomal recessive expressed in childhood and characterized by markedly elevated (> 30 fold) plasma levels of plant sterols [10, 52, 53]. This is due to both hyperabsorption of plant sterols from intestine into liver and their inefficient excretion from liver into intestine (Fig. 1) [10, 52, 53]. Sitosterolemic individuals also absorb a higher percentage of dietary cholesterol than normals, and they secrete less cholesterol into bile, which increases the hepatic cholesterol pool, decreases LDLR activity and in turn increases LDL-C [10, 52, 53] (Fig. 1). The molecular defects responsible for sitosterolemia are caused by mutations in two genes that encode two half-transporters, ABCG5 and ABCG8 [10, 52, 53]. Their two genes on chromosome 2p are located in a head-to-head orientation. ABCG5 and ABCG8 are expressed exclusively in human liver and intestine, the sites of the two metabolic abnormalities in sitosterolemia (Fig. 1). The normal dual functions of ABCG5 and ABCG8 are to limit the absorption of cholesterol and plant sterols and promote their excretion from liver into bile (Fig. 1).

The diagnosis of sitosterolemia is considered, and plant sterols measured, in any child or adolescent who has xanthomas despite disproportionately low LDL-C (from <130 to 400 mg/dL, which can be normal, moderately elevated, or markedly elevated, depending on the dietary content of cholesterol and plant sterol [52]. Adults with undiagnosed sitosterolemia can clinically mimic FH heterozygotes. CVD can present in the first or second decade of life but is usually delayed until early to middle adulthood. Patients with sitosterolemia may develop aortic stenosis, as do those with homozygous FH [10, 52, 53]. Hemolysis and thrombocytopenia are also found [52, 53].

Mutations in Proprotein Convertase Subtilisin-like Kexin Type 9 (PCSK9). PCSK9 is a serine protease that promotes the degradation of LDLR [54]. Gain-of-function mutations that increase PCSK9 activity decrease LDLR activity, yielding a phenotype that mimics FH [12, 54]. Secreted PCSK9 binds to the LDLR at the cell surface, leading to the internalization of a LDLR/PCSK9 complex via clathrin-mediated endocytosis and then routed to lysosomes via a mechanism that does not require ubiquitination or ARH, and is distinct from the classic autophagy and proteosomal degradation pathways [12].

Deficiency of Cholesterol 7α-Hydroxylase. An autosomal co-dominant disorder affecting cholesterol 7α hydroxylase activity, the first enzyme in the classical pathway for bile acid biosynthesis (Fig. 1), was described in three homozygotes with a deletion mutation in *CYP7A1* [55]. The homozygotes had LDL-C levels similar to those found in FH heterozygotes. One of the adult homozygotes had premature CVD. The heterozygotes for the CYP7A1 mutation had LDL-C levels in between the homozygotes and the normal unaffected relatives [55]. The TG were also elevated in the homozygotes. No xanthomas were reported.

A block in the conversion of cholesterol to bile acids via this rate limiting enzyme would theoretically decrease secretion of cholesterol in bile from the liver and increase the hepatic pool of cholesterol leading to downregulation of LDLR and HMG-CoA reductase (Fig. 1). Despite the increased cholesterol in bile, the cholesterol content of liver was increased two fold in these homozygotes, indicating that a functional ABCG5/ABCG8 in liver could not compensate for this defect in conversion of cholesterol into bile acids [55] (Fig. 1).

Treatment of FH, FDB, ARH and PCSK9 Disorders

Dietary Management. A stringent diet reduced in total fat to <30 % and in saturated fat to <8 % of calories with negligible trans fat and cholesterol to <200 mg/day is the

foundation of the diet. Reduction in LDL-C by such dietary management is modest, about 10 %. Plants sterols as margarines (e.g., Benecol and Take Control) can decrease the absorption of cholesterol from the diet, and importantly from biliary cholesterol, resulting in an increase in LDLR and an additional fall in LDL-C of about 10 %.

Pharmacologic Management. The statins are the first form of drug treatment in each of these four disorders. The response is usually quite impressive (30–40 %) with the starting dose of the statin (Table 2) chosen in FH, FDB, PSCK9 heterozygotes, and ARH homozygotes. Increasing the statin to higher doses results in an additional decrease of about 6 % in LDL-C for each dose escalation [10, 23]. A second agent, either a BAS or ezetimibe, will be required to lower the LDL-C further. The patient may require triple therapy by adding niacin to decrease LDL production, an effect independent of inducing LDLR. Inhibitors of PCKS9 have great promise as additional LDL lowering agents, which in combination with statins can lower LDL-C another 50 % [41] or permit statin-resistant patients to be well-treated.

FH homozygotes respond modestly (about 25 %) to higher doses of potent statins (Table 2), due to reduced cholesterol and VLDL reduction; comparing the pre-statin to post-statin eras, a significant reduction in CVD events and mortality has been reported in South African homozygotes [56]. Addition of ezetimibe (approved by FDA for FH homozygotes) can produce another 25 % decrease in LDL-C [57]. BAS may have a modest effect on LDL-C. Some FH homozygotes respond well to niacin (55–87 mg/kg/day in divided doses for children), which reduces hepatic production of TG leading to decreased VLDL and LDL levels (see above). Almost all FH homozygotes will require LDL apheresis weekly in addition to drug treatment to effect a satisfactory reduction in LDL-C [22]. Liver transplants are not routinely performed in FH homozygotes because of the long-term complications of the procedure and of the possibility that the surgery may lower LDL but not prevent significant coronary atherosclerosis [58]. In contrast to FH homozygotes, homozygotes for ARH manifest a dramatic response to statins alone, or when combined with CAI, ezetimibe [51].

Treatment of Phytosterolemia

The dietary treatment of sitosterolemia differs importantly from the other disorders affecting LDLR. *Both* cholesterol and plant sterols must be markedly reduced. The LDL-C levels can vary considerably, e.g., from a normal to 500 mg/dL, depending on the sterol content of the diet. Saturated fats are also restricted. Vegetable oils (canola oil, olive oil) and their derivatives, such as margarines, must be avoided because of their high plant sterol content.

Pharmacologic Treatment. Statins are less effective in sitosterolemia since HMGCoA reductase activity is already reduced to about 12 % of normal and 7 alpha hydroxylase is reduced 30 % [59] (Fig. 1). Both bile aid sequestrants [60] and ezetimibe [61] are quite effective, and when used in combination may produce marked improvement in plasma sterol concentrations, increased platelets, disappearance of xanthomas and carotid bruits, and decrease in murmur of aortic stenosis [62].

Treatment of 7 α Hydroxylase Deficiency

The hypercholesterolemia in the three homozygous with 27 α hydroxylase deficiency did not respond to statins alone, most likely due to the increased cholesterol pool in these patients [55]. Both the hypercholesterolemia and hypertriglyceridemia in these patients responded well to a combination of a statin and niacin [55].

Disorders of Overproduction of VLDL and LDL

Syndromes of VLDL and LDL Overproduction. This is the major metabolic abnormality in: familial combined hyperlipidemia (FCHL), hyperapobetalipoproteinemia (hyperapoB), and LDL subclass pattern B, familial dyslipidemic hypertension and syndrome X of Reaven [63]. The lipid phenotypes of these disorders are pleiotropic but their common denominator is an increased number of LDL particles (> 75th %, Table 1) that are mostly small and dense. Other aspects of this lipid phenotype (also referred to as atherogenic lipid phenotype) are variably present and include: hypercholesterolemia: hypertriglyceridemia; elevated apoB (> 120 mg/dL, 75th %, Table 1) with normal (< 130 mg/dL) or borderline LDL-C (130 to 159 mg/dL) (< 75th %); and low HDL-C (< 40 mg/dL). Non-lipid components of these disorders can include: obesity; insulin resistance; type II diabetes; glucose intolerance; hypertension, and CVD [63]. The "metabolic syndrome" includes hypertension, glucose intolerance, high triglycerides, low HDL-C, and increased waist circumference [63]. No assessment of elevated LDL-P is currently part of the assessment of the metabolic syndrome.

No single molecular genetic defect has been definitely elucidated to explain any of these disorders and the expression of these phenotypes are most likely due to the influence of oligogenic factors [64]. Several loci that regulate apoB levels have been identified. Variations of the activity or the expression of various nuclear factors (upstream stimulatory factor 1(USF1), transcription factor 7-like 2 (TCF7L2), hepatocyte nuclear factor 4 (HNF4alpha) that regulate the expression of multiple genes involved in the metabolism of lipids or carbohydrates have a major role in the pathophysiology of FCHL.

Metabolic Basis of FCHL, HyperapoB and Other Small, Dense LDL Syndromes. A 2–3 fold increased production of the TG-rich VLDL requires enhanced biosynthesis of TG, availability of CE, and decreased apoB-100 degradation (leading to increased apoB-100 production) (Fig. 1). Increased flux of FFA occurs in FCHL and hyperapoB and other small dense LDL syndromes [63–66]. This increased mobilization of FFA usually is secondary to impaired insulin-mediated suppression of hormone sensitive lipase in adipocytes. Such insulin resistance is particularly prominent in the visceral adipocyte, from which the FFA flux directly to the liver through the portal vein without being exposed first to the peripheral circulation. This paradigm may also result from a defect in the normal effect of the acylation stimulatory protein (ASP), which is to stimulate the incorporation of FFA into TG in the adipocyte [67]. If the flux of FFA exceeds the capacity of the hepatocytes to oxidize FFA, then increased biosynthesis of TG occurs. Excess FFA also interferes with the normal effect of insulin, which is to decrease cholesterol synthesis, CE availability and increase apoB-100 degradation.

The increased secretion of VLDL stimulates the activity of CETP, resulting in an enhanced transfer of TG from VLDL for CE on LDL and HDL (Fig. 2). Activity of HL increases, hydrolyzing the TG in LDL and HDL, producing small, dense LDL and smaller HDL (Fig. 1). The VLDL remnants contain more CE per molecule, producing a more atherogenic remnant particle. Finally, elevated TG-rich VLDL compete with chylomicron and their remnants for LPL, often resulting in delayed removal of these particles.

Treatment of Disorders of VLDL Overproduction

Hygienic Measures. Restriction in simple sugars lowers TG and is a paramount addition to the standard low fat diet, which decreases the burden of post-prandial chylomicrons and atherogenic chylomicron remnants (Fig. 1). A decrease in dietary saturated fat and cholesterol can decrease LDL by up regulating LDLR. Loss of weight improves insulin sensitivity, decreases the mobilization of FFA, leading to a decrease VLDL overproduction and TG. Regular aerobic exercise (1000 calories /week) is important for weight reduction since many patients have a low basal metabolic rate and cannot lose weight unless they exercise.

Pharmacologic Measures. If the TG are >500 mg/dL, the TG elevation is addressed first. Niacin, fibrates, and fish oils (Steps 4, 5, and 6, respectively, Fig. 1) lower TG significantly (24, 24, and 38–40) (Table 2). HDL-C often increases and sLDL-P- are converted into larger LDL-P [63]. If the TG are <500 mg/dL, the statins are the drug of choice since they are the most effective in lowering LDL-C and, in particular, the LDL-P and sLDL-P [24]. Statins also increase removal of IDL through the LDLR (Fig. 1).

Most patients with VLDL overproduction require combined lipid-altering therapy, most often a statin combined with one of the three TG reducing agents [23, 24, 30, 40]. If a patient is statin-intolerant, TG are first lowered with a fibrate, and then a BAS or ezetimibe added [30, 33]. BAS should not be used as the initial drug in patients with VLDL overproduction since they can increase TG. If the HDL-C is notably low after statin treatment, niacin is the second drug of choice [35••]. In patients with impaired glucose tolerance (IGT), diabetes, or insulin resistance, metformin can lower TG, FBS, insulin and weight in patients with VLDL overproduction. Glitazones are not recommended because of their potential adverse side effects.

Disorders of Exogenous Hypertriglyceridemia

Three inherited defects result in profound hypertriglyceridemia due to markedly deficient LPL activity: defective or absent LPL; abnormal apoC-II, the co-factor for LPL (Fig. 1); and, deficiency in glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1). Other defects involving chylomicron metabolism include: homozygous loss- of-function mutations in *APOA5* and frameshift mutations in caveolin-1 [3, 68•].

Defective or Missing Lipoprotein Lipase. LPL deficiency is a rare recessive trait causing profound hypertriglyceridemia (as high as 10,000 mg/dL), due to massive increases in chylomicrons and the inability to clear dietary fat [3, 68•]. Marked hypercholesterolemia, e.g., 300 to 1000 mg/dL is also often present, secondary to the hyperchylomicronemia, and thus the patient will have a ratio of TG to TC of at least 5 and usually 10. VLDL-C is normal, and HDL-C and LDL-C are low. Obligate heterozygous parents of affected children are often consanguineous and have normal lipid levels, or a moderate hypertriglyceridemia. To date, more than 80 mutations in the LPL gene have been reported [68•]. Missense mutations typically predominate in the LPL gene, with a preferential location in exons 3, 4, and 5, and in the catalytic triad, Asp_{156}, His_{241}, and Ser_{132}.

The diagnosis of LPL deficiency requires a determination of lipolytic activity in plasma after the intravenous injection of heparin (60 U/kg), which releases the membrane-bound lipases into the bloodstream [postheparin lipolytic activity (PHLA)]. The total lipolytic activity and HL activity are determined and the LPL activity calculated. HL activity is normal and LPL markedly decreased. The level of apoC-II is normal, as judged by immunochemical methods.

The disorder usually presents early in the first year of life. Often creamy blood is noted in a hematocrit tube or when blood is being drawn. Abdominal pain is a common symptom, presenting as colic in the first year of life or as an acute

abdominal condition later in childhood. Other clinical features may include eruptive xanthomas, hepatosplenomegaly, and lipemia retinalis. Premature atherosclerosis does not occur in LPL deficiency since large chylomicrons do not enter the vascular wall and are therefore not atherogenic.

Defects in Apolipoprotein C-II. When a deficiency of apoC-II (the cofactor for LPL) is present, hypertriglyceridemia can range from 800 to almost 10,000 mg/dL; the elevated chylomicrons may be expressed alone or accompanied by elevated VLDL [68•]. TC can also be normal or increased (about 150 to 1000 mg/dL). The LDL and HDL-C levels are below the fifth percentile of normal persons (Table 1). The disorder is rare and inherited as an autosomal recessive. Abnormalities of the apoC-II gene are caused by either small deletions or by splice-site mutations [3, 68•]. LPL activity is absent or very low. ApoC-II is present in only trace amounts. The problem usually presents in adulthood with pancreatitis, although one homozygote developed pancreatitis at the age of 6 years.

Defective GPIHBP1. GPIHBP1 is anchored in endothelial cells and "picks-up" LPL from interstitial spaces and shuttles it across endothelial cells to the capillary lumen [69]. When GPIHBP1 is absent, hypertriglyceridemia can be severe. As well mutations in either GPIHBP1 or LPL that affect the ability of either to bind to each other can cause hypertriglyceridemia [69]. PHLA is very low.

Reduced ApoA-V. Levels of apoA-V are negatively correlated with TG. ApoA-V may normally stimulate proteoglycan-bound LPL at the endothelium of capillaries [70]. A number of molecular variants in apoA-V are associated with low apoA-V and higher TG levels; the aggregation of five variants can be associated with TG of >1000 mg/dL [68•].

Disorders of Endogenous Hypertriglyceridemia

Familial Hypertriglyceridemia (FHT). In some families' plasma TC, LDL-C, apoB, and LDL-P will clearly be normal, chylomicrons absent and VLDL-C and TG levels elevated (> 95th %, Table 1). Males have considerably higher TG cut points than females [68•] (Table 1). FHT is distinguished from FCHL by normal LDL-C, LDL-P and apoB in the affected parent and siblings of the proband because their VLDL are not being overproduced but their TG are hydrolyzed abnormally. LPL and apoC-II are normal. HDL-C can be low or normal. Adults with FHT manifest glucose intolerance, obesity, hyperuricemia, peripheral vascular disease (PVD) and to a lesser extent CVD. FHT *may be* inherited as an autosomal dominant trait with delayed penetrance [68•].

Disorders of Combined Exogenous and Endogenous Hypertriglyceridemia

Elevated Chylomicrons and VLDL. The lipid phenotype of marked hypertriglyceridemia is due to increased chylomicrons and VLDL. Common clinical findings include pancreatitis, eruptive xanthomas, lipemia retinalis, and IGT with insulin resistance. Chylomicron- and VLDL- remnants promote CVD and PVD. Increased VLDL may result from increased synthesis or decreased clearance, or a combination of both. The full-blown phenotype is usually expressed in adults. Affected relatives may have endogenous hypertriglyceridemia alone, or combined with exogenous hypertriglyceridemia. Autosomal dominant inheritance was reported in several large kindreds.

Dysbetalipoproteinemia (Type III Hyperlipoproteinemia). Patients with "dysbeta" present with elevated TC and TG, each often >300 mg/dL. Cholesterol-enriched VLDL, with β rather than pre-β electrophoretic mobility and a VLDL-C to TG ratio usually >0.3 (normal, 0.15–0.25) define dysbeta [71]. Cholesterol-enriched remnants from both VLDL and chylomicrons accumulate. LDL-C, LDL apoB and HDL-C levels are usually low [71]. Diagnosis requires beta quantification by preparative ultracentrifugation and determination of apoE phenotype [71].

Human apoE exists as three major isoforms (E_2, E_3, and E_4), each of which is specified by an independent allele at the locus for *APOE*. There are six possible genotypes: *APOE2/E2; APOE2/E3, APOE3/E3, APOE3/E4, APOE4/E4 and APOE2/E4*. One in 100 persons is homozygous for *APOE2/E2*, a necessary but insufficient genotype for dysbeta [71]. Since the prevalence of dysbeta is rarer (1:10,000), other modifying factors, such as an overproduction of VLDL (seen in FCHL), hypothyroidism, low-estrogen state, obesity, or diabetes are necessary for the full-blown clinical expression. The phenotype of dysbeta results from decreased binding of apoE_2 on TG remnants to LDLR combined with overproduction of VLDL [71]. This recessive form of dysbeta has a delayed penetrance.

One of several rare variants of apoE express the dominant form of dysbeta. The single substitution of a neutral or acidic amino acid for a basic residue within AA sequence 136 to 150—prevents apoE from binding to the LDLR [71]. Examples are: Arg142Cys; Arg145Cys; Lys146Gln or Glu. The dominant form can be expressed in childhood and does not require the presence of modifying factors.

Patients with dysbeta often develop xanthomas, particularly yellowish deposits in the creases of the palms of the hands (xanthoma striata palmaris) and tuberous and tuberoeruptive xanthomas over the elbows, knees, and buttocks [71]. Tendon xanthomas are less frequent. Premature atherosclerosis of the coronary, carotid, abdominal, and femoral arteries is

prevalent. Hyperuricemia and glucose intolerance occur in up to half the patients with this syndrome.

Of interest, apoE4 is associated with increased risk for atherosclerosis, Alzheimer's disease, impaired cognitive function, and reduced neurite outgrowth [72]. ApoE3 is the wild type allele.

HL deficiency. Marked deficiency in HL reduces hydrolysis of TG and PL in IDL, LDL and large HDL (Figs. 1 and 2), affecting both apoB-containing and apoA-I containing lipoproteins. Decreased clearance of both post-prandial TG and IDL occurs, leading to large B-VLDL (similar to dysbeta), hypertriglyceridemia >500 mg/d and hypercholesterolemia. Decreased hydrolysis of TG and PL on HDL produces elevated large, TG-enriched HDL particles [73]. LDL-C level is normal but TG enriched. HL activity is determined by a test of PHLA activity (see also above). HL deficiency is rare <12 families); heterozygotes for HL deficiency exhibit intermittent biochemical characteristics and HL activity [73], influenced by genetic variants, obesity, gender, and diet [73, 74]. Premature CVD is increased and affected patients have responded to statins and fibrates. A common variant in the promoter of the HL gene (C-514T) is strongly associated with increased HL activity and FCHL [74] (see above).

Treatment of Profound Exogenous Hypertriglyceridemia

A stringent restriction in fat to 10 to 15 g/d is required (see also above). Intake of linoleic acid as 1 % of the calories is important. Medium-chain triglycerides (MCT) are absorbed directly through the portal vein and can be added to the diet as 15 % of calories. MCT can increase compliance to the strict low-fat diet and often lower TG to a greater extent than expected. A subset of LPL-deficient patients respond to therapy with MCT oil and omega-3-fatty acids by normalizing fasting TG; a therapeutic trial with MCT oil and fish oils should, therefore, be considered in all patients with LPL deficiency [75]. Standard lipid-altering drugs are ineffective in LPL and apoC-II deficiency. A dramatic reduction in recalcitrant pancreatitis without a reduction in marked hypertriglyceridemia was reported in three patients with documented LPL deficiency in response to daily antioxidant therapy (alpha tocopherol 270 IU /day, beta carotene 9000 IU/day, vitamin E 540 mg/day and selenium 600 ug/day) [76].

Treatment of more Severe Combined Exogenous and Endogenous Hypertriglyceridemia

Treatment starts with a fat restricted diet (see also above), reduction to ideal weight, and when necessary, drug therapy, possibly including the fibrates, omega-3 fatty acids, niacin and the statins (see Steps 1, 4,5,6, Fig. 1). Treatment of 12 patients with primary hyperchylomicronemia for 12 weeks with 4 grams of omega-3-fatty acid esters reduced TG (mg/dL) from 1624 mg/dL (SD 383) to 894 mg/dL (SD 241); LPL activity was not determined [77]. Unlike disorders of exogenous TG metabolism, those of both exogenous and endogenous TG metabolism will respond to treatment with fibrates, fish oils or niacin.

Familial Disorders of HDL Metabolism

The most common cause of the phenotype of low HDL-C levels (hypoalpha) is arguably secondary to VLDL overproduction, and the subsequent expression of high TG, increased sLDL-P and low HDL-C [63]. *Primary* HDL disorders include: familial hypoalphalipoproteinemia (hypoalpha) [78, 79]; homozygous gene deletions or nonsense mutations in apoA-I [15, 78]; missense mutations in apoA-I [79–82]; more than 100 common and rare variants in ABCA1, including the prototype, Tangier disease [83]; and LCAT deficiency [84].

At the other end of the spectrum, there are several familial disorders of HDL metabolism that present with *elevated* HDL-C levels and reduced CVD. These include a deficiency in CETP [15, 78] and familial hyperalphalipoproteinemia (hyperalpha) [6].

Hypoalphalipoproteinemias

Familial Hypoalphalipoproteinemias. The phenotype of hypoalphalipoproteinemia (hypoalpha) is defined as a low level of HDL-C (< 5th %, Table 1) with normal TC, TG, and LDL-C levels. Adults with hypoalpha do not manifest the clinical findings typical of other more malevolent forms of HDL deficiency (see below). Hypoalpha is relatively common perhaps autosomal dominant in some families but oligogenic in most. Familial hypoalpha may be related to increased catabolism or decreased synthesis of apoA-I. Increased incidence of premature CVD is commonly, but not invariably, a feature of this condition. The molecular defect(s) underlying common hypoalpha are not known.

Deletions and Nonsense Mutations in Apolipoprotein A-I. Little if any biosynthesis of apoA-I by liver and intestine occurs in the rare homozygous gene deletions or nonsense mutations resulting in premature truncation [15, 78] (Fig. 2). The virtual absence of apoA-I in plasma results in marked reduction in HDL-C. Obligate heterozygotes and homozygotes develop premature CVD. Homozygotes can also manifest retinopathy, cataracts, and tendon xanthomas.

Missense Mutations in Apolipoprotein A-I. A number of apoA-I variants due to specific amino acid substitutions are known [15, 78–82]. These missense mutations in apoA-I are

associated with low HDL-C, but do not generally increase risk of CVD. In one instance, apoA-I Milano, there is a decrease in CVD in families whose members have a mutation in the apoA-I gene at codon 173, which changes arginine to cysteine and alters the structure of apoA-I. The disulfide bond of this cysteine forms dimers with apoA-II and other proteins [81]. Low HDL-C levels are due to increased turnover of apoA-I. Recombinant ApoA-I-Milano was injected intravenously each week for six weeks and reduced coronary atherosclerosis in adults with acute coronary syndromes, as judged by intravascular ultrasound [82].

Tangier Disease. Dr Donald Fredrickson described two affected young sisters with large orange tonsils and virtually absent HDL and apoA-I over 50 years ago on Tangier Island in the Chesapeake Bay. *APOAI* in Tangier patients was normal [83]. A defect in cholesterol efflux from Tangier fibroblasts leads to poor lipidation of apoA-I and its rapid removal by the kidney. Linkage studies in multiple kindreds and molecular cloning in three laboratories demonstrated that the basic defect resided in a double-dose of mutations in a previously described ATP-binding cassette (ABCA1) transport protein [83]. ABCA1 was subsequently shown to be essential for the initial step in reverse cholesterol transport (Fig. 2) to form a nascent HDL particle (Fig. 2). Reticuloendothelial cells likely sequester chylomicron-like lipoprotein particles rich in CE, present in the density range of HDL on a normal high-fat diet, causing large tonsils, hepatosplenomegaly and deposition in bone marrow. These lipoproteins disappear on a low-fat diet. Early atherosclerosis and CVD can occasionally occur but are not major components of Tangier disease.

Lecithin-Cholesterol Acyltransferase Deficiencies and Fish-Eye Disease. Esterification of cholesterol by LCAT, and its co-factor apoA-I, produces a spherical HDL (Fig. 2). Mutations in LCAT provide important insights into the pathophysiology of the next step in reverse cholesterol transport. LCAT esterifies cholesterol through association with HDL (α-LCAT) or, to a lesser extent, with VLDL/LDL (β-LCAT). In classic LCAT deficiency, both α-LCAT and β-LCAT activities are absent, resulting in a markedly reduced plasma cholesterol esterification rate, a low plasma CE content, and an abnormal lipoprotein profile with a very low HDL [84]. The marked reduction in HDL reflects a failure to form mature spherical HDL, leading to increased catabolism of the nascent HDL particle. Clinical findings include glomerulosclerosis, normochromic anemia, and corneal opacities (that can be detected in childhood). Coronary disease is not prevalent although premature peripheral atherosclerosis has been reported. Specific defects in the LCAT gene, including stop codons and amino acid substitutions, have been elucidated in several kindreds with classic LCAT deficiency [84].

Fish-eye disease is a phenotypically distinct syndrome of LCAT deficiency in which most, but not all, patients appear to have a selective defect in α-LCAT activity, which is accompanied by dense corneal opacities; low HDL-C, but premature atherosclerosis is not present. Several molecular defects such as $LCAT^{300\text{-}del}$ have been described in the LCAT gene of patients with fish-eye disease [84].

Hyperalphalipoproteinemias

Familial Hyperalphalipoproteinemia. The phenotype of hyperalpha is defined as an HDL-C level >95th percentile, for age and gender (Table 1). LDL-C is often normal. Family members with hyperalpha often have reduced CVD and longevity [85]. Hyperalpha is genetically heterogeneous. Segregation of mutations in *LIPG, CETP, SR-B1* and *GALNC2* occurs in Caucasian families with extremely high HDL cholesterol [85].

CETP Deficiency. In disorders of VLDL overproduction, increased CETP activity results in a smaller HDL with less CE (see also above). Conversely, if CETP activity is decreased, HDL will be larger and enriched in CE. Homozygous CETP deficiency is expressed as markedly increased HDL-C levels (generally >120 mg/dL) [86]. The most prevalent CETP mutations have been described in Japan. Heterozygous for CETP deficiency exhibit 60–70 % of normal CETP activity, modest increases in HDL-C, and normal LDL-C levels. The relationship of CETP mutations to atherosclerotic risk is not completely resolved [86].

Scavenger Receptor Class B Type I Receptor Deficiency. SR-BI selectively takes up CE from HDL [87, 88]. SR-B1 is regulated by a number of factors. Single nucleotide polymorphisms (SNPs) in the *SCARB1* gene are significantly associated with HDL-C levels [87] and subclinical carotid atherosclerosis [88].

Deficiency of Endothelial Lipase. Endothelial lipase (EL) belongs to the triglyceride lipase family that includes LPL and HL (Figs. 1 and 2). EL is a product of *LIPG* and mostly hydrolyses PL in HDL with less TG lipase activity, converting HDL from a larger to a smaller particle (Fig. 2). Rare loss-of-function EL variants produce a higher HDL-C but such an increase in HDL-C does not reduce CVD [89].

Treatment of Disorders of HDL Metabolism

Hygienic measures (see above) can increase HDL-C by about 10 mg/dL. Each of the lipid-altering drugs (steps 1 through 6 in Fig. 1) can increase HDL-C, albeit to different degrees (Table 2). Other drugs such as beta-blockers can

decrease HDL-C and substitutions should be made when clinically feasible.

Of the lipid-altering drugs that increase HDL, niacin is the most effective, followed by fibrates and statins. The effect of these agents as well as the hygienic measures may fail to raise HDL in a patient who has a mutation that profoundly affects the biosynthesis, intravascular remodeling, or degradation of HDL. Nevertheless, a low fat diet has other beneficial effects in Tangier disease and LCAT deficiency (see above).

Elevated Levels of Lp (a) Lipoprotein

Lp (a) lipoprotein (or apo (a) lipoprotein) is very large (M_r 3×10^6) and mostly found in the HDL density range [90•]. The lipid composition of Lp (a) is similar to LDL, but Lp (a) contains two proteins, apoB-100 and a large glycoprotein called apo (a). Apo (a) is attached to apoB-100 by a disulfide bond [90•]. Apo (a) is quite homologous to plasminogen but has no protease activity. Lp (a) levels are 90 % inherited and depend on the apo (a) gene on chromosome 6q27. Lp (a) enters the vascular wall, and elevated Lp (a) is a causal risk factor for CVD. The precise physiological function of Lp (a) is unknown. Lp (a) promotes thrombosis and stroke in children [22] and adults, through the inhibition of conversion of plasminogen to plasmin at the surface of endothelial cells [90•]. Lp (a) also binds oxidized PL promoting inflammation and CVD [90•].

Diagnosis and Treatment of Lp (a) Lipoprotein. Lp (a) is measured by an ELISA assay using a monoclonal antibody. The upper limit of normal <75 nmol/L. Niacin and estrogen lower Lp (a) levels, while the statins and fibrates do not. The effect of specifically lowering Lp (a) to prevent CVD has not been proven. Patients with CVD and elevated Lp (a) are treated more aggressively with a statin to reduce their LDL-C level to <100 mg/dL (Table 2) Niacin can be used to reduce Lp (a) and increase HDL-C.

Deficiencies in ApoB-containing Lipoproteins

These disorders are discussed briefly here related to their relevance to lipid and lipoprotein metabolism. They are not associated with premature CAD.

Hypobetalipoproteinemia

Patients with primary hypobetalipoproteinemia (hypobeta) are defined by very low levels of LDL-C, usually less than the lower fifth percentile of normals (Table 1). TC is low; VLDL-C and TG are low or normal. Hypobetalipoproteinemia can be *secondary* to anemia, dysproteinemias, hyperthyroidism, intestinal lymphangiectasia with malabsorption, myocardial infarction, severe infections, and trauma.

Familial Hypobeta. Familial hypobeta is inherited as an autosomal dominant. Most of the mutations in *APOB* are either nonsense or frame shift mutations that produce a premature stop codon and a truncated apoB-100 [91]. The apoB-100 produced by the normal allele is reduced to about 25 % of normal, while the truncated apoB is cleared too rapidly from plasma [91], resulting in decreased apoB-100, VLDL and LDL (Fig. 1). Hepatic fat is increased about three fold. Those with familial hypobeta are usually asymptomatic, their prevalence of CVD is low and often longevity is found. Familial hypobeta is also linked to a susceptibility locus on chromosome 3p21, and in some families is linked neither to *APOB* nor to chromosome 3p21.

Familial Combined Hypolipidemia. Two nonsense mutations in the angiopoietin-like 3 gene (*ANGPTL3*) on chromosome 4 resulted in markedly decreased LDL-C accompanied by notably low TG and HDL-C, a phenotype termed familial combined hypolipidemia [92]. LDL-C and TG levels were inherited as co-dominant traits while the low HDL-C was only present in the genetic compounds. This novel finding in this large family suggests a new mechanism for decreasing LDL-C in patients.

Loss of Function Mutations in PCSK9. Hypobeta is also present in those with a loss-of-function mutation in the PCSK9 gene [11, 93]. Here, low LDL results not from decreased production of LDL but from increased LDLR activity resulting from decreased degradation of LDL through the LDL/PCSK9 pathway [11]. Those with such familial hypobetalipoproteinemia have an up to 80 % lifetime reduction in CVD.

Abetalipoproteinemia (abeta) (Bassen-Kornzweig syndrome). Abeta is a rare autosomal recessive disorder whose clinical expression starting in childhood includes fat malabsorption, severe hypolipidemia, retinitis pigmentosa, cerebellar ataxia, and acanthocytosis [94]. Each of the major apoB-100 containing lipoproteins (chylomicrons, VLDL, and LDL) is absent from plasma, resulting in low levels of both cholesterol and triglyceride. Both apoB-48 and apoB-100 are absent. Parents have normal lipid phenotypes.

Abeta is not caused by a defect in *APOB* [8, 22, 94]. The absence of a functional 97-kDa subunit of MTP in both liver and intestine, causes a failure in the intracellular transport of membrane-associated lipids and their association with apoB, (Fig. 1), producing a defect in the synthesis and secretion of apoB.

The clinical findings result from defects in absorption and transport of the fat-soluble vitamins A, E, and K [8, 22, 94]. Vitamin E requires chylomicrons to reach the liver, after which it is secreted on VLDL and subsequently ends up in LDL (Fig. 1). The significant impairment in the delivery of vitamin E to peripheral tissue is the most clinically important fat-soluble vitamin deficiency in patients with abeta, and most of the major symptoms, particularly of the retina and nervous system, appear to be the result of vitamin E deficiency [22, 94].

Treatment of Abetalipoproteinemia

Fat intake is reduced to 5 to 20 g/d [94], resulting in decreased steatorrhea, marked clinical improvement and growth acceleration. The diet is also supplemented with linoleic acid (e.g., 5 g corn oil or safflower oil/d). MCT as a caloric substitute for long-chain fatty acids may produce hepatic fibrosis, and thus MCT should be used with caution, if at all. Fat-soluble vitamins should be added to the diet. Rickets can be prevented by normal quantities of vitamin D. Neurologic and retinal complications may be prevented, or ameliorated, through oral supplementation with vitamin E.

Chylomicron Retention Disease CRD or Anderson's Disease. CRD is a rare recessive disorder that causes failure to thrive, malnutrition, growth failure, vitamin E deficiency and other complications [95, 96]. The diagnosis is made based on chronic diarrhea with fat malabsorption, very decreased but not absent LDL-C and apoB and normal TG [95, 96]. Vitamin E deficiency and fat-laden enterocytes are invariably present. Hepatic steatosis is common. Muscular complications are manifested by increased creatine kinase levels and cardiomyopathy. In contrast to abeta, there is no retinitis pigmentosa and little acanthocytosis. Mutations in *SAR1B*, leading to a defective Sar1b protein prevent the normal transport of prechylomicrons from the ER to the Golgi [95, 96]. No postprandial chylomicrons or apoB-48 are detected. On institution of a low-fat diet supplemented with lipid soluble vitamins (A and E) and essential fatty acids, normal growth resumes with reduction of gastrointestinal symptoms. Departure from a low-fat diet results in rapid relapse and recurrence of symptoms. Essential fat*y* acid deficiency is especially severe early in life. Especially large amounts of vitamin E are necessary to prevent neurological complications.

Conclusions

The lipoprotein field is mature and many defects of familial dyslipoproteinemia have been elucidated. Some like FCHL will be encountered routinely in practice while others are rare. Unusual patients can be evaluated and treated by considering the major pathways of lipoprotein metabolism and their clinical ramifications. Consultation with a lipid specialist can be helpful.

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- • Of importance
- •• Of major importance

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