LIPOPROTEINS

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BRIEF HISTORY OF CHOLESTEROL AND ATHEROSCLEROSIS

There is a long history of a relationship between cholesterol and atherosclerosis. Vogel first identified the deposits of cholesterol in the artery wall in 1840s [1, 2]. The German pathologist Felix Jacob Marchand first introduced the descriptive term “atherosclerosis” in 1904 to describe the “gruel-like” fatty substance buildup inside a hardened artery and suggested that atherosclerosis is responsible for obstructive processes in the arteries [3]. However, the causal relationship between cholesterol and atherosclerosis was not clarified until 1910s by a series of laboratory experiments that were initiated by an accidental discovery when they studied the role of diet in aging [4, 5]. Feeding rabbits with meat or egg yolk induced atherosclerosis, while feeding the animals with egg white did not produce atherosclerosis [5]. Based on these observations, the investigators concluded that meat and egg yolk play a critical role in atherosclerosis formation. Sobolev et al. performed a systematic survey to evaluate factors in meat and egg yolk that could lead to atherosclerosis [5], and Anitschkow and Chalatow in 1913 continued the work by feeding rabbits with purified cholesterol that resulted in the development of typical atheromatous lesions in rabbits [3, 5, 6]. These and subsequent studies led Anitschkow to the conclusion that “there is no atherosclerosis without cholesterol” [7]. These series of experimental studies established the causal relationship of dietary cholesterol to the development of atherosclerosis in rabbits and marked the beginning of the modern era of atherosclerosis research.

Cholesterol is a hydrophobic lipid that is not solubilized by the aqueous environment of the
plasma and is therefore transported by macromolecular complexes known as lipoproteins. In 1929, Macheboeuf first isolated a stable, water-soluble lipoprotein by precipitation from horse serum [8, 9]. This lipoprotein contains 59% protein and 41% lipid, which consisted of 18% cholesterol and 23% phospholipid and could be re-dissolved in water to form a clear solution. Macheboeuf called it lipid-containing α-globulin at the time, and it is now recognized as high-density lipoprotein (HDL). The development of the ultracentrifuge by Svedberg in the 1920s provided an important laboratory instrument for the flotation and isolation of lipoproteins. In the 1930s, by using ultracentrifugation, McFarlane first noticed a time- and salt-dependent layer that existed between the albumin and globulin layers. He named it “X-fraction” [10], which was later named low-density lipoprotein (LDL) [9, 11]. In 1941, Blix separated α- and β-globulins by paper electrophoresis [12], which is now replaced by more advanced technology with agarose gel electrophoresis.

Among those who tried to characterize the full spectrum of lipoproteins in blood, the American medical physicist John W. Gofman was the first to successfully achieve this goal [13]. Later Gofman and colleagues also provided important epidemiologic evidence that cholesterol-carrying molecules (lipoproteins) in the blood predicted the risk of heart disease [14]. Gofman’s work opened the window on the complexity of the lipoproteins and sparked the explosive increase in the attention of the research on the plasma lipoproteins and their relationship to atherosclerosis. Ancel Keys postulated a correlation between cholesterol levels and cardiovascular disease (CVD) and initiated a study of Minnesota businessmen (the first prospective study of CVD), demonstrating an association of blood cholesterol with CVD [15]. He subsequently extended this observation to several other countries in a study known as the Seven Countries Study [16]. In 1965, Frederickson and Lees in the National Institutes of Health (NIH) used more advanced technology for lipoprotein electrophoresis and developed a system of lipoprotein phenotypes [17], later refined by Frederickson and Levy [18] to a classification of hyperlipoproteinemias that remains in use to this day. The Framingham Heart Study, a long-term prospective study of cardiovascular risk factors definitively established that incident coronary artery disease (CAD) risk is highest in groups with highest blood cholesterol levels at baseline [19]. Participants with total cholesterol greater than 245 mg/dl at baseline had a three-fold increased risk of incident coronary heart disease (CHD) compared with participants with a total cholesterol less than 210 mg/dl.

LIPOPROTEINS

Lipoproteins are large macromolecular complexes that transport hydrophobic lipids in the blood. Lipoproteins consist of a core of hydrophobic lipids (triglycerides [TGs] and cholesteryl esters) surrounded by a shell of hydrophilic lipids (phospholipids and unesterified cholesterol) and proteins. The plasma lipoproteins are divided into five major classes based on their relative density: chylomicrons (Figure 1.1), very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), LDL, and HDL. The density of a lipoprotein is determined by the amount of lipid per particle. The proteins associated with lipoproteins, called apolipoproteins, are required for the assembly, structure, and function of lipoproteins. Apolipoproteins activate enzymes, mediate lipid transfer, and act as ligands for cell surface receptors. Apolipoprotein-B (apoB) is the major structural protein of chylomicrons, VLDL, IDL, and LDL; whereas apoA-I is the major protein in HDL particles [20].

LDL AND ATHEROSCLEROSIS

Metabolism of LDL

LDL is derived from the lipolysis of TGs in VLDLs, which are secreted by the liver (Figure 1.2). The rates of VLDL production
and lipolysis of VLDL TG influence plasma levels of LDL cholesterol (LDL-C). However, the most important determinant of plasma LDL-C is the rate of LDL catabolism by the liver. This is primarily influenced by the abundance and activity of the LDL receptors on the surface of the hepatocytes. The LDL receptor is regulated by cellular cholesterol content at both transcriptional and post-transcriptional levels. In addition, the protein proprotein convertase subtilisin/kexin type 9 (PCSK9) is secreted by the liver and targets the LDL receptor for degradation, thereby providing another layer of regulation. High levels of LDL-C are generally a result of reduced LDL receptor expression due to genetic or environmental influences or both.
Epidemiology

There is a strong positive association between plasma levels of LDL-C and risk of CHD across many populations and ethnic groups. In epidemiologic studies, every 1 mg/dl increase in LDL cholesterol is associated with a 2% increased risk for CVD [21]. There is a continuous, graded relationship between LDL-C levels and subsequent risk for cardiovascular disease. This association does not itself prove that LDL is causal for atherosclerosis. However, there are a number of lines of evidence in humans that support the causality of LDL, including single-gene inherited conditions of high and low LDL-C, common variants associated with LDL-C and CHD, and intervention studies of LDL-C reduction leading to reduction in CV events.

Inherited Conditions Causing Elevated LDL-C Are Associated with Increased CHD and Those Causing Reduced LDL-C with Reduced CHD

Single-gene inherited disorders causing substantially elevated levels of LDL-C are unequivocally associated with premature CHD. Familial hypercholesterolemia (FH) is caused by loss-of-function mutations in the LDL receptor [22]. Heterozygous FH is characterized by substantial elevations in LDL-C (usually >200 mg/dl) and premature CHD. Homozygous FH, caused by mutations in both LDL receptor alleles, is characterized by markedly elevated cholesterol (usually >400 mg/dl) and markedly accelerated atherosclerosis starting in childhood. The discovery of FH provided strong evidence that LDL is causally linked to atherosclerotic disease.

Other single-gene causes of elevated LDL-C also increase the risk of CHD. Familial defective apoB-100 (FDB) [23] is caused by mutations in the receptor-binding region of apoB-100 that impair its binding to the LDL receptor and delay clearance of LDL. Like heterozygous FH, FDB is associated with elevated LDL-C and premature coronary disease [23]. Gain-of-function mutations in the PCSK9 gene also cause elevated LDL-C and premature CHD [24]. PCSK9 binds to cell surface LDL receptors in the liver and promotes their lysosome degradation rather than recycling of the receptor [25]. Gain-of-function mutations in PCSK9 enhance the ability of the PCSK9 protein to bind to the LDLR, which reduces the number of cell surface LDL receptors. Interestingly, loss-of-function mutations in this gene cause low LDL-C levels and reduced risk of CHD (see the following text).

Familial hypobetalipoproteinemia is a condition of low LDL-C due to mutations in apoB that reduce secretion and/or accelerate catabolism of apoB [26]. This condition is associated with reduced risk of CHD. Further, loss-of-function mutations in PCSK9 cause low LDL-C levels [27, 28] and are associated with a lifelong reduction in CHD [29]. These two conditions strongly support a causal role for LDL in atherosclerosis and that lower levels of LDL-C over a lifetime substantially reduces CHD risk. These conditions have also provided genetic support for the development of new LDL-lowering therapies. Mipomersen is an antisense oligonucleotide targeting the apoB mRNA in liver. It reduces LDL-C levels in humans [30] and is approved for use in patients with homozygous FH. PCSK9 inhibition with antibodies is highly effective in substantially reducing LDL-C levels in humans [31] and has emerged as another potential new therapeutic strategy to lower LDL-C that is still in clinical development.

Common Variants Associated with LDL-C Are Generally Associated with CHD in the “Right Direction”

Genome-wide association studies (GWASs) of common DNA variants have identified dozens of loci associated with LDL-C levels, including both “known” genes and “novel” genes. These studies have substantially reinforced the evidence that LDL-C plays a strong causal role in CHD. For example, the majority of LDL-C loci were significantly associated with CHD with concordant directionality, that is, variants associated with higher LDL-C were associated with increased risk of CHD [32]. Further, a
GWAS meta-analysis for CHD, detailed a total of 46 independent loci that were genome-wide significant and 20% of these loci were also genome-wide significantly associated with LDL-C in the direction concordant with CHD risk [33, 34]. This discovery of a major enrichment of “LDL-C genes” in an experiment focused on genes associated with CAD further confirms the indisputable causal relationship between LDL-C levels and CAD.

**Interventions That Reduce LDL-C Levels Reduce CHD Events**

There is now a very large body of evidence based on randomized controlled trials indicating that intervention to reduce LDL-C levels reduces cardiovascular events [35]. Most of these studies involve HMG-CoA reductase inhibitors (statins), although other approaches to reducing LDL-C have also been shown to reduce events. A detailed review of these studies is beyond the scope of this chapter. However, these data strongly support the observational epidemiology, single-gene conditions, and common variant genetics in supporting the causal role of plasma LDL-C levels in atherosclerotic CVD.

**TRIGLYCERIDE-RICH LIPOPROTEINS AND ATHEROSCLEROSIS**

**Metabolism of Triglyceride-rich Lipoproteins**

Triglyceride-rich lipoproteins (TRLs) are synthesized by both the intestine and the liver. Dietary lipids are absorbed in the small intestine and packaged with apoB-48 to form chylomicrons that are secreted into the intestinal lymph and delivered directly to the systemic circulation (Figure 1.1). In peripheral tissues such as adipose and muscle, lipoprotein lipase (LpL) hydrolyzes the TGs in chylomicrons—an effect that creates chylomicron remnants that are rapidly removed from circulation by the liver through a process that requires apoE as a ligand for receptors in the liver. The liver esterifies free fatty acids to TGs and incorporates them into VLDL particles that contain apoB-100 and are secreted into the plasma (Figure 1.2). As with chylomicrons, the TGs of VLDL are hydrolyzed by LPL in muscle and adipose tissue creating VLDL remnants or IDLs. The liver removes approximately half of IDL particles by LDL receptor-mediated endocytosis via binding to apoE. The remainder of the IDL is remodeled by hepatic lipase (HL) to form LDL.

**Epidemiology**

The independent relationship of TG levels and cardiovascular disease has been a topic of debate over the years; but recently, a general consensus has developed that TGs are an independent predictor of cardiovascular risk [36]. In addition, single-gene conditions and common variant studies support a causal role for at least some types of TRLs in atherosclerosis. However, interpretation of the observational epidemiology and genetic studies is complicated by the heterogeneity of TRL and the likelihood that certain TRLs (such as chylomicrons) are not atherogenic, whereas other TRLs (such as VLDL remnants) are highly atherogenic.

**Inherited Conditions Influencing TGs Are Variably Associated with CHD**

Single-gene disorders associated with elevation in chylomicrons alone are probably not associated with increased CHD. The familial hyperchylomicronemia syndrome (FCS) is caused by homozygosity for loss-of-function mutations in one of two genes encoding the protein LPL and apoC-II [37]. FCS is characterized by extreme hypertriglyceridemia (>1000 mg/dl) usually presenting in childhood with acute pancreatitis, eruptive xanthomas, lipemia retinalis, and/or hepatosplenomegaly. Interestingly, despite markedly elevated TG (and cholesterol) levels, premature atherosclerotic cardiovascular disease is not generally a feature of this disease, suggesting that chylomicrons themselves are not atherogenic.
On the contrary, genetic conditions that increase chylomicron and VLDL-remnant lipoproteins appear to be associated with increased CHD risk. Familial dysbetalipoproteinemia (FD), or type III hyperlipoproteinemia, is caused by mutations in the gene for apoE [38]. ApoE on chylomicron and VLDL remnants normally mediate their catabolism by binding to receptors in the liver. FD is usually caused by homozygosity for a common variant called apoE2, which differs from the wild-type apoE3 form by a substitution of a cysteine for an arginine at position 158. ApoE2 has impaired binding to lipoprotein receptors such as the LDL receptor, resulting in defective removal of chylomicron and VLDL remnants. Importantly, premature atherosclerotic CVD is common in this disorder, an observation that helped to clarify that remnant lipoproteins are highly atherogenic.

**Common Variants associated with TG Levels Are Variably Associated with CHD**

There are a number of loci in the genome that are strongly associated with plasma TG levels. Many are also associated with LDL-C, and the majority of these are also associated with CHD. One TG locus not associated with LDL-C but strongly associated with CHD is the LPL locus. The gain-of-function variant (rs264 leading to S447X) is associated with reduced TG, elevated HDL-C, and significantly reduced risk of CHD [32, 33]. Alternatively, another variant (rs12678919) is associated with increased TG, reduced HDL-C, and increased CHD risk [39]. Thus, the actions of LPL modulate TG (and HDL-C) levels, thereby directly influencing CHD risk. While this does not prove that TRLs are causally pro-atherogenic, it supports the concept.

**Interventions That Reduce TG Levels Do Not Consistently Reduce CHD Events**

There are a much smaller number of randomized controlled trials with interventions that reduce TG levels (primarily fibrates and omega-3 fatty acids or fish oils). A detailed review of these studies is beyond the scope of this chapter. The fibrate studies have yielded mixed results but on balance have been disappointing [40]. The fish oil trials have not been designed specifically as TG-lowering trials. Importantly, none of the trials with fibrates or fish oils were specifically performed in subjects selected for elevated TG levels at baseline. Ultimately, trials of TG-lowering drugs in individuals with elevated TG levels will be needed to address the causal role of plasma TG levels in atherosclerotic CVD.

**HDL AND ATHEROSCLEROSIS**

**Metabolism**

HDL metabolism is complex. Nascent HDL particles are synthesized by the intestine and the liver (Figure 1.3). Newly secreted apoA-I rapidly acquires phospholipids and unesterified cholesterol from its site of synthesis (intestine or liver) via efflux promoted by the membrane protein ATP-binding cassette protein A1 (ABCA1). Within the HDL particle, the cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT) to cholesteryl ester and the HDL becomes spherical. HDL cholesterol is transported to hepatocytes through two pathways. HDL cholesteryl esters can be transferred to apoB-containing lipoproteins in exchange for TG by the cholesteryl ester transfer protein (CETP). The cholesteryl esters are then removed from the circulation by LDL receptor-mediated endocytosis. HDL cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class B1 (SR-B1), a cell surface receptor that mediates the selective transfer of lipids to cells. HDL particles also undergo remodeling by a variety of lipid transfer proteins and lipases. The phospholipid transfer protein (PLTP) has the net effect of transferring phospholipids from other lipoproteins to HDL. After CETP-mediated lipid exchange, the TG-enriched HDL becomes a much better substrate for hepatic lipase (HL), which hydrolyzes the TGs and phospholipids to generate smaller HDL particles. Endothelial
lipase (EL) hydrolyzes HDL phospholipids, generating smaller HDL particles that are catabolized faster.

HDLs are very heterogeneous with regard to size and density, lipid composition, and apolipoprotein composition. While there has been considerable interest over the years in the relationship of subfractions of HDL based on size and density, there are no compelling data to support any HDL subfraction having significantly greater predictive power than HDL-C itself. The nature of the apolipoproteins on HDL could be a determinant of differential relationship to CHD. For example, apoC-III-containing HDLs have been reported to lack the inverse association with CHD and have properties in vitro consistent with a pro-atherogenic profile.

Epidemiology

The inverse association between HDL-C and CHD has been repeatedly and consistently noted in scores of observational studies across the world and is one of the most consistent epidemiologic observations with regard to cardiovascular risk. In epidemiologic studies, every 1 mg/dl increase in HDL cholesterol is associated with a 2–3% decreased risk of CHD [21]. While the association is unquestioned, there remain substantial questions about the causal nature of this association. Neither the inherited conditions nor the common genetic variant studies support a causal role for HDL in influencing CHD risk.

Inherited Disorders Causing Low HDL-C Are Generally Not Associated with Increased CHD

Missense or nonsense mutations that result in structurally abnormal or truncated apoA-I proteins cause low HDL-C but are not generally associated with an increased risk of atherosclerosis [41]. Only complete genetic deficiency of apoA-I has been associated with increased CHD. Tangier disease is caused by

Figure 1.3 Schematic diagram of HDL metabolism. ABCA1, ATP-binding cassette transporter A1; ABCB11, ATP-binding cassette transporter B11; ABCG1, ATP-binding cassette transporter G1; ABCG5/8, ATP-binding cassette transporter G5 and G8; A-I, apolipoprotein A-I; CE, cholesterol ester; CETP, cholesteryl ester transfer protein; EL, endothelial lipase; FC, free cholesterol; LCAT, lecithin-cholesterol acyltransferase; PLTP, phospholipid transfer protein; SR-BI, Scavenger receptor class B member 1.
loss-of-function mutations in both alleles encoding the gene adenosine triphosphate-binding cassette protein A1 (ABCA1) [42]. It is characterized by cholesterol accumulation in the reticuloendothelial system causing enlarged orange tonsils, hepatosplenomegaly, intestinal mucosal abnormalities, and peripheral neuropathy, as well as markedly low HDL-C (<5 mg/dl) and apoA-I levels [42]. However, patients with Tangier disease do not develop rapidly accelerated atherosclerosis to the extent one might expect based on the cholesterol efflux defect and the extremely low HDL-C levels. Heterozygotes for ABCA1 mutations have reduced HDL-C levels that are intermediate between Tangier disease and normal but have no evidence of cholesterol accumulation in tissues. Mutations in ABCA1 have been found to cause low HDL-C levels in some families in which Tangier disease homozygotes are not found [43], and these individuals are also not at increased risk of CHD. Finally, LCAT deficiency is caused by loss-of-function mutations in both alleles of the LCAT gene [44]. LCAT is the enzyme that esterifies the free cholesterol present in HDL to cholesteryl ester, creating a cholesteryl ester core and resulting in maturation of HDL. In the absence of functional LCAT and cholesteryl esterification, mature HDL particles are not formed and nascent HDL particles containing apoA-I are rapidly catabolized [45]. Interestingly, LCAT deficiency is not clearly associated with premature coronary disease, despite the markedly reduced HDL-C levels [44].

CETP deficiency is caused by loss-of-function mutations in both alleles of the CETP gene [46]. CETP transfers cholesteryl esters from HDL to apoB-containing lipoproteins in exchange for TGs. Lack of functional CETP results in markedly elevated HDL-C levels due to lack of HDL remodeling, accumulation of cholesteryl esters in HDL, and slower turnover of apoA-I [47]. Whether homozygous or heterozygous, CETP deficiency is associated with increased, decreased, or unchanged cardiovascular risk that remains to be resolved.

**Common Variants Associated with HDL-C Alone Are Generally Not Associated with CHD**

The association of HDL-C loci with CHD is much less consistent than for LDL-C loci. Many common variants associated with HDL-C are also associated with LDL-C or TG levels, making them unsuitable tools for assessing the causal relationship of HDL-C to CHD. Testing this hypothesis for the CETP locus is of particular interest as drug development programs targeting this protein are ongoing. Thompson et al. [48] conducted a meta-analysis of studies reporting on the relationship between CETP gene variants, HDL cholesterol, and risk for CHD. Three common CETP variants were associated with increased HDL-C and weakly associated with decreased CAD risk to the degree predicted by observational epidemiology data. However, multiple variants at this locus were also found to be significantly associated with LDL-C and TGs in addition to HDL-C; therefore, the possibility that the CAD-associated CETP variants exert their effect on cardiovascular disease risk through changes in LDL-C or TG levels cannot be excluded. As noted earlier, ABCA1 is an important regulator of plasma HDL-C levels. Interestingly, variants in ABCA1 associated with lower HDL-C levels were not found to be associated with increased risk of CHD [49]. However, many of these variants are also associated with lower LDL-C levels.

Thus, the efforts to address this question have focused on genetic variants that are specifically associated with HDL-C and not LDL-C or TG. As noted earlier, LCAT is a key enzyme that regulates HDL metabolism and HDL-C levels. Low-frequency variants at the LCAT locus associated with reduced HDL-C were found to have no association with increased CHD risk [50]. Endothelial lipase (EL; gene name LIPG) hydrolyzes HDL phospholipids and accelerates HDL catabolism and has been shown in mice to be an important regulator of HDL-C levels [51]. Deep candidate gene re-sequencing of the LIPG gene in
subjects with extremes of HDL-C identified rare, nonsynonymous loss-of-function variants in subjects with extremely high HDL-C levels not found in persons with low HDL-C [52]. In addition, a low-frequency (~2% minor allele frequency) loss-of-function variant, N396S, was shown to be associated with significantly elevated HDL-C levels [52]. In a very large analysis, this variant was confirmed to be associated with a significant increase in HDL-C but no association with other lipid or nonlipid risk factors [32]. While observational epidemiology would have predicted a significant reduction in myocardial infarction (MI) risk based on the HDL-C increase, there was no association of this variant with CHD risk. In the same analysis, 14 additional HDL-C variants that were not associated with changes in other lipids were also found to have no association with CHD [32]. Overall, these aggregated results provide poor support for the concept that plasma HDL-C levels are causally associated with atherosclerotic disease.

**Interventions That Increase HDL-C Levels Have Not Been Shown to Reduce CHD Events**

There are only a few randomized controlled trials with interventions that raise HDL-C levels (primarily niacin and CETP inhibitors), but they have not supported the “HDL cholesterol hypothesis.” A detailed review of these studies is beyond the scope of this chapter. Two studies of niacin added to a statin both showed increases in HDL-C but failed to demonstrate a reduction of CV events [53]. Two different CETP inhibitors, torcetrapib and dalcetrapib, raised HDL-C substantially but failed to reduce CV events [54, 55]. There remains substantial interest in the concept that HDL composition, for example, content of apoC-III [56], or HDL function, for example, capacity to promote cholesterol efflux, may be causally more relevant than HDL-C levels per se [57] and that therapeutically targeting “HDL flux” might reduce CV risk [58]. In addition, the post-translational modification of apoA-I can directly lead to HDL dysfunction as observed, for example, in HDL from diabetic subjects [59]. Ultimately, trials of interventions that promote cholesterol efflux and reverse cholesterol transport will be needed to address this hypothesis.

**SUMMARY**

Lipoproteins are important risk factors for atherosclerotic CVD. LDL-C is clearly an independent risk factor and all available evidence indicates that LDL-C is a causal factor in promoting atherosclerosis and cardiovascular events. Plasma TG levels are probably an independent risk factor as well, and the evidence suggests that certain TRLs, particularly remnant lipoproteins, are causal whereas others, particularly chylomicrons, are not. Finally, HDL-C is a major independent inverse risk factor for CHD. However, available evidence suggests that this strong association may not be causal in nature. LDL-C, TG, and HDL-C can all be used to predict risk of CHD, but data currently exist only for intervention targeted toward reducing LDL-C as a strategy to reduce risk of cardiovascular events.

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