Chapter

Introductory Chapter: Overview of Lipoprotein Metabolism

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1. Introduction into lipids

Dyslipidemia is a major cardiovascular disease (CVD) risk factor that is frequently encountered in clinical practice, affecting one in three adults (over 30% of adult population) in the United States alone [1, 2]. It is generally associated with other CVD risk factors including insulin resistance/diabetes, hypertension, and central obesity. With the publication of the landmark observational study, the Framingham Heart Study, the predictive relationship between hypercholesterolemia and coronary heart disease (CHD) was established, where adults with total cholesterol (TC) of >300 mg/dl were 5 times more likely to have CHD, compared with those of TC of <200 mg/dl [3]. These findings were further supported by data from another landmark study, the Multiple Risk Factor Intervention Trial (MRFIT) that clearly demonstrated a graded and strongly positive correlation between TC levels and CHD mortality [4]. Subsequently, multiple trials using various lipid-lowering agents clearly established CVD benefits from lipid lowering. For example, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), using cholestyramine, a bile acid sequestrant, demonstrated that 1% reduction in TC led to 2–3% reduction in CHD risk [5]. Similarly, using gemfibrozil, a fibric acid derivative, in the Helsinki Heart Study, a 5-year primary prevention trial, there was 34% risk reduction in myocardial infarction and sudden cardiac death in the treatment group, compared to placebo [6]. With the advent of statins, numerous clinical trials have shown CVD benefits with cholesterol-lowering therapy that are above and beyond just lowering lipid levels [7]. These findings collectively reinforced the negative connotation associated with lipids in general, despite the vital roles lipids play in various metabolic processes such as the bi-lipid layer cell membrane, the formation of steroid hormones, and bile. In this introductory chapter to our book that addresses topical issues of dyslipidemia, we provide an introduction we believe will be useful to a wide range of audiences including students, researchers, and clinical providers with a simplified overview of the structure, classification, and metabolism of lipids. This chapter will serve as a quick and illustrated reference to the reader of this book, Dyslipidemia, thus facilitating the understanding of the other book chapters.

2. Classification of lipids

There are three types of lipids:
Simple lipids such as oil and waxes.
Complex lipids such as phospholipids, glycolipids, and lipoproteins.
Derived lipids such as steroid hormones and lipid-soluble vitamins.

3. Saturated and unsaturated fatty acids

Saturated fatty acids are those containing no double bonds such as acetic (CH_3—COOH) and palmitic acid (**Figure 1**).

Unsaturated fatty acids contain one or more double bonds and are divided into three categories: **Monounsaturated** (one double bond), **polyunsaturated** (two or more double bonds), and **eicosanoids** (derived from 20 carbons = eicosa) that include **prostaglandins**, **thromboxanes,** and **leukotrienes.**

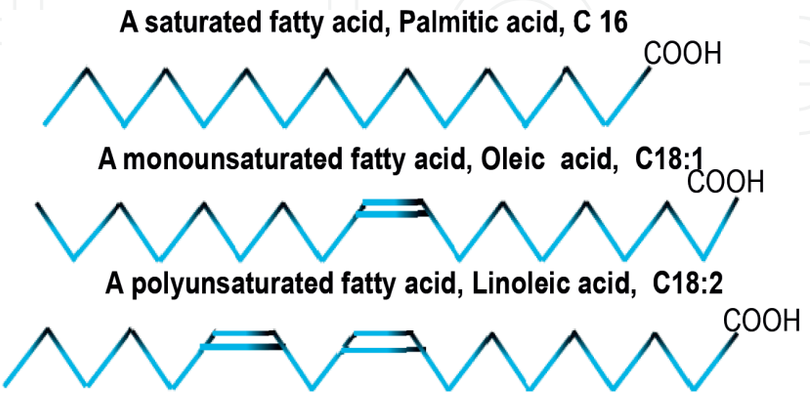

Figure 1.
Saturated and unsaturated fatty acids.

4. Cis and trans bonds

Cis and trans bonds are isomers of fatty acids (**Figure 2**); nearly, all naturally occurring bonds are in cis configuration. Trans fatty acids are the results of partial hydrogenation, a process that is used to create solidified products such as margarine. Trans fatty acids are proinflammatory, increase LDL and decrease HDL-cholesterol, and increase risk for obesity, diabetes, and CVD. These deleterious effects of trans fats prompted the FDA to ban the production of partially hydrogenated oils in June 2018. **Figure 2** illustrates how trans fats can stack neatly, one on top of the other, to create dense solid fats.

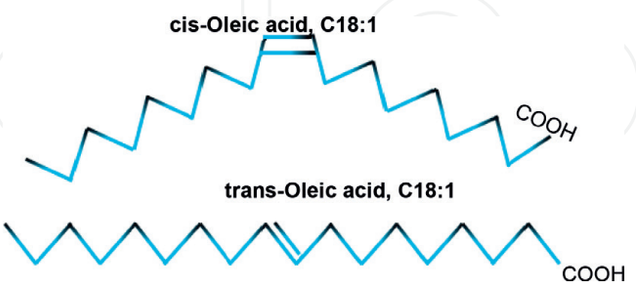

Figure 2.
Cis- and trans-oleic acid.

5. Overview of lipoprotein structure, function, and metabolism

Lipids are insoluble in water and are transported in the plasma (or extracellular fluids) by lipoproteins. These lipoproteins have, in their basic structure, a lipid core to be transported (triacylglycerols (TAG), phospholipids, and cholesterol esters). A hydrophilic layer in which apolipoproteins are embedded thus provides structural stability as well as identity for each type of the lipoprotein.

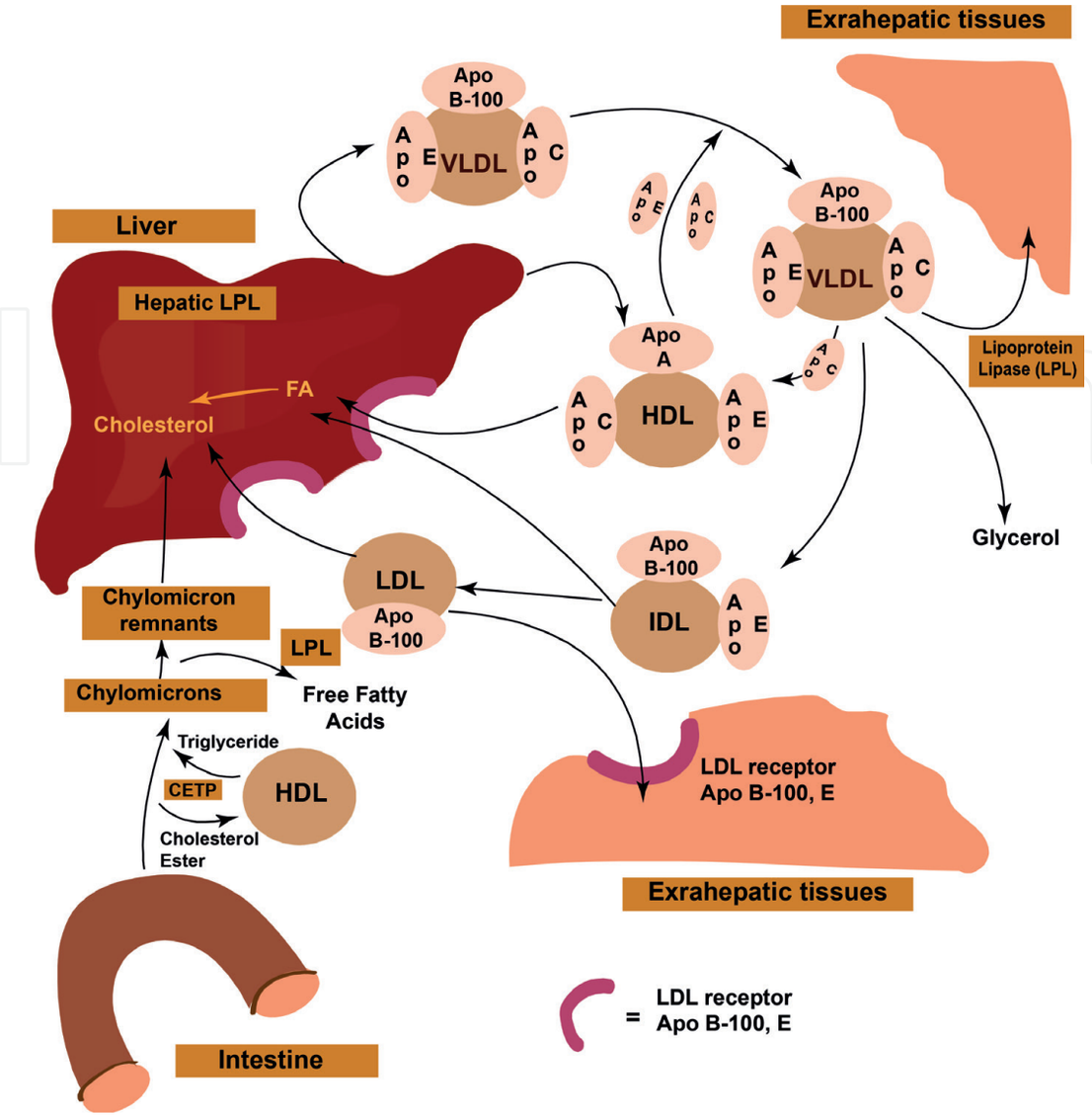

Figure 3.
Lipid transport and storage.

There are five major types of lipoprotein (**Figure 3**), classified based on their density (hence their size) from ultra-low-density lipoprotein (ULDL = chylomicrons) to very-low-density lipoprotein (VLDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL). Chylomicrons (CM) are the largest in diameter with the lowest density and the highest TAG content.

Lipoprotein lipase is an enzyme that cleaves VLDLs and TAGs. TAGs are cleaved into free fatty acids and glycerol. Fatty acids eventually undergo **beta-oxidation**, and their energy is used by the heart and skeletal muscles. In the blood, free fatty acids are bound to albumin.

6. Exogenous (intestinal) lipid transport pathway

CM, formed in the intestinal epithelial cells (enterocytes), are the lipoproteins involved in the transport of exogenous (dietary) lipids from the intestine to the lymphatic system into the circulation through the exogenous lipid metabolism pathway (**Figure 3**). These CM contain cholesterol esters (CE) and TAG, formed by re-esterification of FFA, and are carried to the peripheral tissues including muscles and adipose tissues. By the action of activated LPL, FFA are released and undergo beta-oxidation to be used as energy source or stored as fat in the adipose tissues.

CM also, through the action of cholesterol ester transfer protein (CETP), acquire CE from HDL in exchange of TAG. Furthermore, CM in the lymphatic system exchange apo A-I and apo A-II for apo C and E from HDL. Apo C is required for the activation of the LPL, and apo E is required for the recognition of the CM remnants by the liver's receptors (**Figure 3**).

7. Endogenous lipid transport pathway

TAG and cholesterol from CM catabolism (remnants) are endogenously produced in the liver and are secreted in VLDL that contains apo B-100 (**Figure 3**). Similar to the process described above with CM, apo C and apo E are acquired from HDL where apo C activates LPL that catalyzes the hydrolysis of TG in VLDL producing FFA that are taken up by the muscles for energy production or stored in the adipose tissues. And again, as with CM, through the action of CETP, VLDL exchange cholesterol for TAG with HDL resulting in the formation of IDL which can be taken up by the liver via the apo E/remnant receptor or further reduced by hepatic lipase into LDL.

LDL contains only one apoprotein (B-100) and is taken up by the liver through LDL receptors with approximately one-third utilized by peripheral cells for membrane formation and steroidogenesis.

8. Reverse cholesterol transport pathway

This process involves the mobilization of cholesterol from the plasma membranes of cells along the arterial walls and the delivery of the cholesterol to the liver in the form of cholesterol esters (CE), thus reducing cholesterol levels in the periphery and thereby reducing inflammation as well as atherosclerosis.

In the macrophages of the vessel wall, CEs are hydrolyzed via cholesterol ester hydrolase (CEH), thereby releasing free cholesterol. This free cholesterol is transported outside the macrophages via adenosine triphosphate-binding cassette transporter A1 (ABCA1) to apolipoprotein A1, forming nascent pre-β HDL. The free cholesterol is then esterified into CEs via lecithin-cholesterol acyltransferase (LCAT), and the nascent pre-β-HDL then becomes mature α-HDL which converts into mature α-HDL subtypes, α-HDL2 and α-HDL3. This process occurs in the vessel walls as well as in the plasma and is mediated by LCAT as well as hepatic lipase (HL) and endothelial lipase (EL). Mature α-HDL2 and α-HDL3 continue to acquire free cholesterol delivered from inside the cells via ABCG1, therefore increasing the amount of cholesterol carried to the liver via the CE-rich α-HDL via either direct or indirect pathways (**Figure 4**).

In the direct hepatic cholesterol uptake pathway, CE-rich α-HDL binds to scavenger receptor B1 (SR B1) that recognizes Apo A1, and CEs are taken by hepatocytes and excreted in bile. In the indirect hepatic cholesterol uptake pathway, CE-rich α-HDL exchanges CE for TAG from the TAG-rich LAD and VLDL particles, a process that is facilitated by CETP, thereby forming a TAG-rich HDL and CE-rich LDL and VLDL. CEs are then taken by hepatocytes via LDL receptors, catabolized, and also excreted in the bile, as with the direct pathway.

The processes described above are well regulated in healthy states and are quite abnormal in dyslipidemia, leading to excess CVD as well as other disorders such as nonalcoholic fatty liver disease (NAFLD), among others.

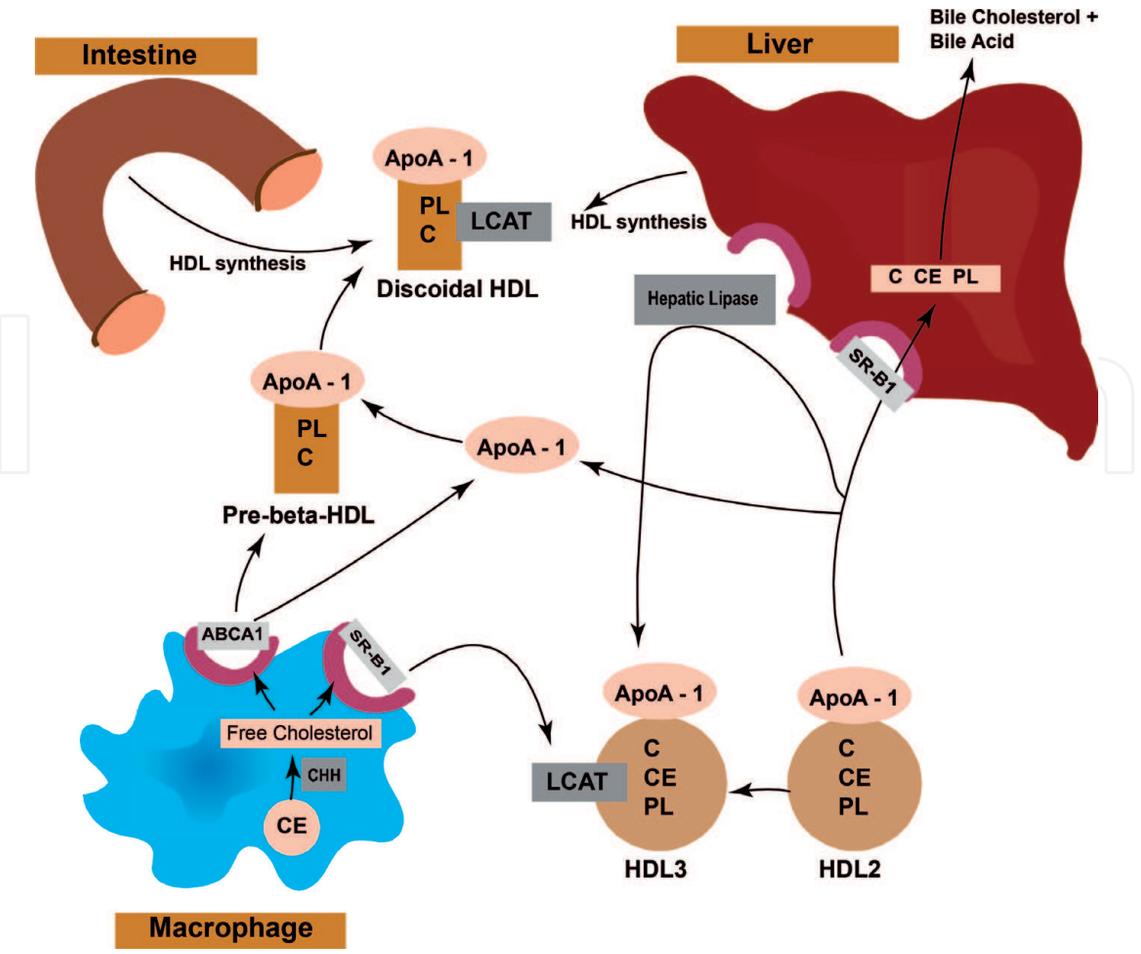

Figure 4.
Reverse cholesterol transport pathway. C, cholesterol; CE, cholesteryl ester; LCAT, lecithin cholesterol ethyl transferase; PL, phospholipid; ApoA-1, apolipoprotein A-1.

Certain disease states interfere with lipid transport pathways, leading to serious disorders. For example, in diabetes mellitus, relative insulin resistance causes under-utilization of VLDLs and chylomicrons, eventually leading to hypertriacylglycerolemia and increased small-density LDLs which promotes atherosclerosis [8]. Among many other roles, insulin inhibits the release of free fatty acids (FFA) from the adipose tissues and suppresses hepatic VLDL secretion into the circulation. These mechanisms come into play in the role of diabetes as a risk factor for CVD including stroke [8].

Furthermore, the inability to suppress VLDL-triglyceride kinetics has been implicated in the pathogenesis of nonalcoholic fatty liver disease [9], a serious complication that leads to CVD, cancer, and liver fibrosis and increases mortality [10].

9. In conclusion

In this short introductory chapter, we provided a brief overview of lipid metabolism highlighting the role of lipids as CVD risk factors, the various types of lipid structure and function as well as the exogenous (intestinal), and the endogenous lipid transport pathways through which fats are transported from the intestines and the liver, respectively, to the peripheral tissues. We also highlighted in some detail the reverse cholesterol transfer pathway via which cholesterol, in the form of cholesterol esters, are transported from the blood vessel walls and other tissues back to the liver for excretion in the bile.

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