4.1.1

Lipid and Lipoprotein Processing

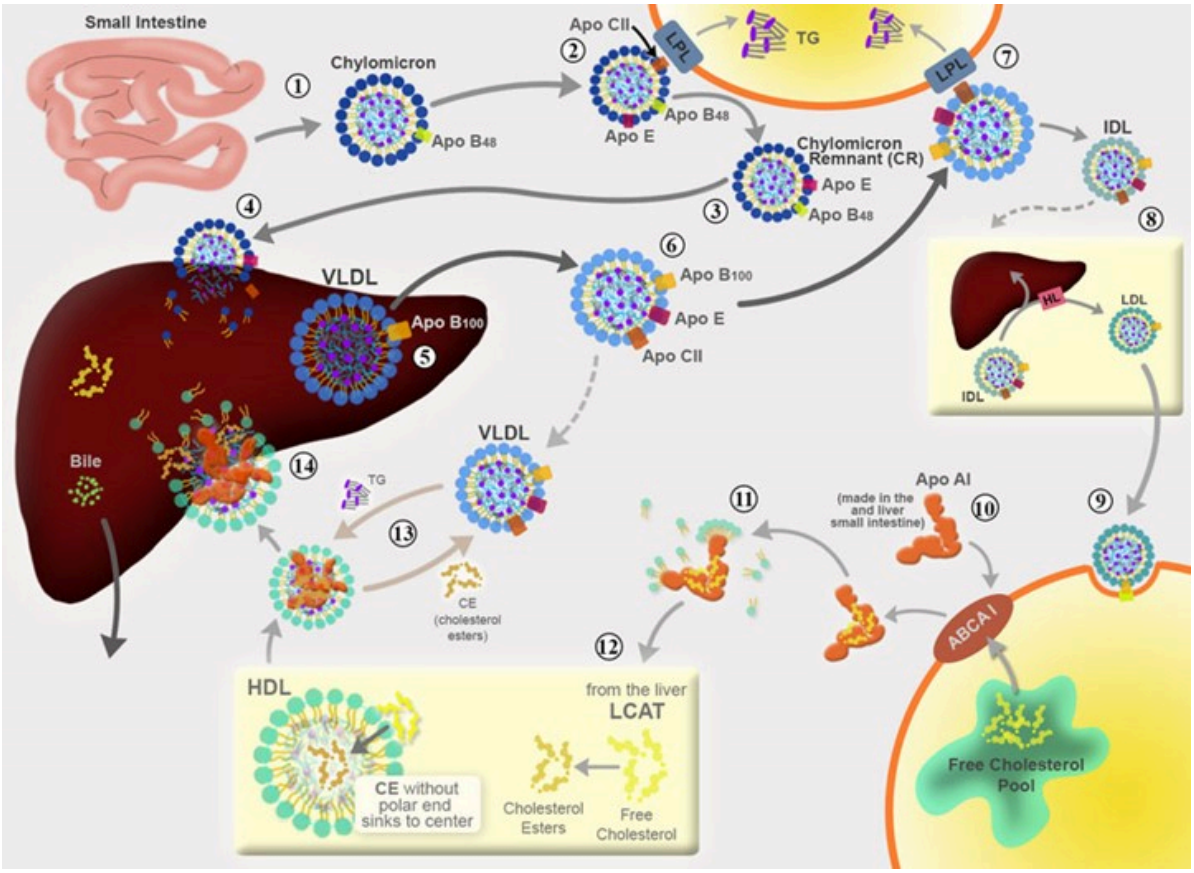
What happens to the fat that we eat? In this section we will discuss in detail the processes that occur when we eat fatty foods and how fat distribution relates to heart health.

Lipid Digestion, Absorption, and Chylomicrons

Please watch Lipid & Lipoprotein Processing Part 1 - Lipids and Chylomicron Formation and Lipid & Lipoprotein Processing Part 2 - Chylomicron Metabolism

Dietary fat is composed largely of triglycerides. Triglycerides are made up of one glycerol molecule with three fatty acids attached at each hydroxyl group. Digestion of dietary fat occurs primarily in the small intestine, more specifically in the duodenum. Here, bile (a collection of amphipathic molecules derived from cholesterol produced by the liver) is secreted from the common bile duct and functions to emulsify the ingested triglycerides. Amphipathic means to have both polar and nonpolar regions. Emulsification is the process of breaking down large lipid droplets into smaller droplets suspended in the aqueous intestinal fluid. This emulsification is possible because the hydrophobic (non-polar) portion of the bile salts will associate with the fat to be digested, while the hydrophilic (polar) portion of the bile salts will associate with the surrounding aqueous fluid of the digestive tract. The smaller droplets that result allow for increased surface area for pancreatic lipases to break down the fat. In order to be absorbed by enterocytes, triglycerides must be broken down into monoglycerides (one fatty acid attached to glycerol) and free fatty acids. Lipase enzymes from the pancreas will break triglycerides into diglycerides (two fatty acids attached to glycerol), monoglycerides, and free fatty acids. These broken down triglyceride components along with free-floating cholesterol, phospholipids, lipid soluble vitamins, and bile salts all come together in the duodenum to form a special structure called a **micelle**. Micelles interact with the brush border surface of the enterocyte boundary and dissociate so the monoglycerides and free fatty acids can enter the enterocytes by simple diffusion. Lipases continue to work on the diglycerides from the micelle to break them down into monoglycerides and fatty acids that can also be absorbed. Cholesterol will also go into the enterocyte, but through a transporter called NPC1L1. NPC1L1 can be blocked by an LDL cholesterol lowering agent known as **ezetimibe (Zetia)** to treat hypercholesterolemia.

Once inside the cell, the smooth endoplasmic reticulum of the enterocyte will reassemble the monoglycerides and free fatty acids back into triglycerides. The newly formed triglycerides will join with cholesterol and a protein produced by the enterocyte called **Apo B48** to form a **chylomicron**. The chylomicron is then packaged into a vesicle by the Golgi apparatus and leaves the enterocyte by exocytosis at the basolateral surface. Chylomicrons are too big to immediately enter the blood through the fenestrae of the capillaries. Instead, they enter the lymphatic system through small lymphatic vessels called lacteals. Chylomicrons then pass through the lymph vessels and are eventually emptied into blood vessels near the heart through the thoracic duct. Once in systemic circulation, chylomicrons deliver triglycerides to different cells of the body which then use the fat for energy.



Lipid Processing and Distribution *Image by Tabitha D. BYU-I S15*

Lipid Processing and Distribution – VLDL, IDL, LDL, and HDL

Please watch Lipid & Lipoprotein Processing Part 3 - Formation of LDL and HDL

After chylomicrons (1 in the image above) enter the circulation, they pick up a couple more proteins from the plasma called **Apo CII** and Apo E. Apo CII will be used to help the chylomicron attach to and activate an enzyme found on body cells called **lipoprotein lipase (LPL)**. Similar to lipases in the digestive tract, LPL will hydrolyze triglycerides into two free fatty acids and one monoglyceride which can then be transported into the cell (see 2 in the image above).

As body cells remove triglycerides from the chylomicrons in this fashion, the chylomicron becomes smaller in size. Eventually, the chylomicron will shrink enough that its affinity for Apo CII decreases and Apo CII is lost. This smaller chylomicron is called a **chylomicron remnant**. **Apo B48** and **Apo E** remain on the chylomicron remnant and are used as ligands to bind to receptors in the liver that will trigger endocytosis of the chylomicron remnant. The liver will use the lipids delivered by the chylomicron remnant to synthesize other lipoproteins or to make bile (see 3 and 4 in the image above).

The liver is able to synthesize its own cholesterol and can use lipids that it receives to synthesize lipoproteins called **very low-density lipoproteins (VLDLs)**. The formation of VLDLs is the start of the endogenous pathway of lipid delivery to body cells (meaning that the substance originated in the liver rather than originating from dietary components). The VLDL will have a protein from the liver called **Apo B100**. After the VLDL is released into the circulation it will do several things very similar to what the chylomicrons did. It will pick up Apo CII and Apo E in the plasma. Apo CII will help the VLDL bind and activate LPL enzymes on body cells so that triglycerides can be removed and fed to the cells (see 5, 6 and 7 in the image above). The removal of triglyceride from the VLDL will cause it to get smaller. The resultantly smaller lipoprotein is called an **intermediate-density lipoprotein (IDL)** and has relatively more cholesterol and less triglycerides than a VLDL (because LPL removes triglycerides but leaves behind cholesterol).

The IDLs in the body travel to the liver where about half of them use their Apo E protein to bind receptors and become endocytosed and broken down (similar to chylomicron remnants). The other half binds to a liver enzyme that is similar in function to LDL called **hepatic lipase (HL)**. HL continues to remove triglycerides and shrink the IDL even more. As the IDL shrinks, it loses Apo E and Apo CII and is left as a small lipoprotein that is even more concentrated with cholesterol called a **low-density lipoprotein (LDL)** (see 8 in the image above).

LDLs still have Apo B100. Apo B100 will attach to receptors on body cells where it will trigger endocytosis of the LDL particle (see 9 in the image above). The role of LDLs is to deliver cholesterol to body cells. You may hear LDLs referred to as "bad cholesterol." The cholesterol in an LDL is not any different than the cholesterol found in other parts of the body. However, high LDL levels in the blood do correlate with the development of an arterial vessel disease called atherosclerosis. For this reason, it is best to keep LDL levels in the blood from becoming too high. Individuals may take medications to lower their high LDLs so that atherosclerosis can be prevented. One of the most common classes of medications given for this are called "**statins**" such as atorvastatin (Lipitor).

Another peptide made by the liver is **Apo A1**. Once in circulation, Apo A1 pulls excess cholesterol out of the free cholesterol pool found in cells of the body through a transporter called **ATP Binding Cassette AI (ABCAI)**. The Apo A1 with attached cholesterol will also pick up phospholipids to become a nascent **high-density lipoprotein (HDL)** (see 10 and 11 in the image above). HDLs are sometimes called "good cholesterol" because they take excess cholesterol from cells and help to remove it from the body. Individuals with mutations in genes that code for the ABCA1 transporter have difficulty removing excess cholesterol from cells. These people have very low levels of HDL in their blood. This condition is called **Tangier disease** and generally leads to early onset of atherosclerosis.

The conversion of a nascent HDL to a mature HDL involves **lecithin cholesterol acyltransferase (LCAT)**, an enzyme made by the liver that is free floating in the plasma. It esterifies the free cholesterol in the nascent HDL (which means binding a fatty acid to the cholesterol hydroxyl group). This makes the cholesterol even more hydrophobic so it gravitates to the center of the nascent HDL molecule. This action forms a mature, larger, and spherical HDL (see 12 in the image above).

Cholesteryl ester transfer protein (CETP) is a plasma protein that allows VLDL and HDL to swap triglycerides and cholesterol esters (see 13 in the image above). It may seem counterproductive to move cholesterol back to a VLDL given that we want the HDL to remove excess cholesterol by taking it back to the liver to become bile and expelled. However, it makes sense from an evolutionary point of view that given how hard it is to get cholesterol in the diet (it is an animal product and not a plant product), humans of the past may have benefited from a way to recycle cholesterol. With the help of CETP the HDL swaps some cholesterol for triglycerides with VLDL, but much of the cholesterol is taken back to the liver where it is used to make bile (see 14 in the image above).

Cholesterol Levels

An optimal level of LDL cholesterol is considered less than 100 mg/dL and optimal total cholesterol level is considered less than 200 mg/dL. A desired level of HDL is above 40mg/dL, but they are viewed with a "higher the better" attitude. Some individuals have levels as high as 80 mg/dL which seems to give some protective benefits against atherosclerosis.

Excessively high total cholesterol and LDL levels is referred to as hypercholesterolemia. Hypercholesterolemia can be described as primary or secondary based on the underlying cause:

1. **Primary hypercholesterolemia** is characterized by high levels of cholesterol independent of environmental causes. Genetic predisposition accounts for many types of primary hypercholesterolemia. One of these genetic predispositions is **familial hypercholesterolemia**, which is characterized by defective or deficient LDL receptors. Because their LDLs can't interact with the cells of their body, individuals with familial hypercholesterolemia have high LDL levels. Another condition called familial defective Apo B100 involves a mutation in the LDL receptor ligand or Apo B100. It is clinically indistinguishable from familial hypercholesterolemia and also causes high LDL levels. Both can lead to the formation of **xanthomas**, which are cholesterol deposits that may form in various parts of the body including the skin, tendons, and

cornea. These individuals have an accelerated rate of atherosclerosis and have much higher risks for myocardial infarction and ischemic strokes at a young age.

2. **Secondary hypercholesterolemia** is acquired and may be caused by obesity with high-calorie intake, a sedentary lifestyle, and diabetes mellitus. Excess intake of cholesterol can lead to LDL receptor downregulation on body cells, which in turn increases LDL levels in the blood. Diets high in saturated fats can also increase cholesterol synthesis by the liver and will also lead to downregulation of LDL receptors on body cells. Diets high in sugar, especially fructose, have been shown to increase risk of hypercholesterolemia. Secondary hypercholesterolemia may also be caused by some medications including estrogen therapy and beta blockers.

Diagnosis of hyperlipidemia is dependent on a person's complete lipid profile after fasting for 12 hours. A relatively simple assessment of blood lipids is often done with a small fingertip drop of blood applied to a machine that can use the principles of light bending to assess quantities of circulating lipoproteins. During this test, LDL levels are not actually measured but can be estimated by completing the following formula called the Friedewald equation. In this equation, the (triglycerides / 5) is used to estimate the VLDL lipoproteins.

LDL [mg/dL] = total cholesterol [mg/dL] – HDL [mg/dL] – (triglycerides [mg/dL] / 5)

This type of test is often done on our campus and students sometimes get values that suggest a problem. Given that this test on campus is just mathematically estimating LDL concentrations, interventions including medications should not be started without further testing by one's physician.