Lipoproteins are made up of complexes of lipids and proteins that primarily work as the transport system for cholesterol, triglycerides and other significant lipids needed by the body. Previously, the study of conditions related to problems in the metabolism of lipoproteins has been exclusive only for researchers focusing on lipids. However, it has been integrated into the inquiry of internists and other specialties as many researchers have provided a link between dyslipidemia and other highly prevalent conditions, such as atherosclerosis and fatty liver disease.

Introduction

Along with the development of the knowledge base regarding the pathogenesis of dyslipidemia, comes the many treatment modalities focused on lipid control. Bile acid sequestrants, niacin and fibrates are only among the many drugs used for this purpose.

Overview: Dyslipidemia
Screening and Diagnosis of Dyslipidemia

Dyslipidemia is a collective term referring to a group of diseases that are characterized with an increased level of cholesterols and triglycerides in the blood. A lipid panel is usually used for screening, and is commonly done in the clinics. Due to the relative convenience and routineness of this screening procedure, it is not uncommon for medical students and interns to encounter problems with lipid metabolism in practice. The measurement of lipids in the blood is optimally done with a blood sample extracted from the patient after fasting.

Aside from identifying which components of the lipid panel are elevated, one should also note if the problem in the metabolism of lipids is primary in nature, or if it is caused by something else entirely. Primary causes of increased levels of cholesterols and lipids are generally genetic and are thought to be brought about by genetic mutations.

<table>
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<th>Genetic disorder</th>
<th>Gene defect</th>
<th>Elevated lipoproteins</th>
<th>Transmission</th>
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<td>Lipoprotein lipase deficiency</td>
<td>LPL</td>
<td>Chylomicrons, VLDL</td>
<td>Autosomal recessive</td>
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<tr>
<td>Familial apoC-II deficiency</td>
<td>APOC2</td>
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<td>GPIHBP1 deficiency</td>
<td>GPIHBP1</td>
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<td><strong>Combined hyperlipidemia</strong></td>
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<td>Familial hepatic lipase deficiency</td>
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<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>APOE</td>
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<td><strong>Hypercholesterolemia</strong></td>
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<td>Familial hypercholesterolemia</td>
<td>LDLR</td>
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<td>Familial defective apoB-100</td>
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<td>Sitosterolemia</td>
<td>ABCG5 or ABCG8</td>
<td>LDL</td>
<td>Autosomal recessive</td>
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(Table adapted from Harrison's Principles of Internal Medicine, 19th ed. by Fauci AS, et al.)

Dyslipidemia may also be caused by secondary conditions. Examples of conditions and disorders that could actually raise lipid levels in the blood, without genetic implications in lipid metabolism, are the following:

- High-carbohydrate diet
- Excessive alcohol intake
- Obesity and insulin resistance
- Excessive glucocorticoid levels
Treatment of Dyslipidemia

In the diagnosis and treatment of dyslipidemia, it is important to note which among the components of the said lipid panel is elevated in order to come up with a more specific and efficient approach to treatment. The good thing about this is that the degree of elevation of plasma lipids could actually give health care providers an image of the cardiovascular risks and complications that could arise if the condition is untreated.

Another important thing to note in the management of dyslipidemia is that it can be caused by a magnitude of conditions. In cases of secondary dyslipidemia, one should be sure to manage the underlying cause as well.

Lipid Metabolism

Composition and Classification of Lipid Metabolism

Lipids, by nature, are non-polar and may have problems when it comes to transport along the polar environment provided by plasma, interstitial and lymph fluid; this is where lipoproteins come in. These complexes are internally composed of triglycerides and cholesteryl esters that bind nonpolar substances such as triglycerides, cholesterol and fat-soluble vitamins to and from the tissues. In order for these to traverse the polar highways, it is enveloped by a hydrophilic shell made up of apolipoproteins, phospholipids and unesterified cholesterol.

Lipoprotein particles are composed of a lipid core containing cholesteryl esters and triglycerides, and a surface coat of phospholipids, unesterified cholesterol, and apolipoproteins.

Lipoproteins vary in the proportion of their components and their function. These complexes may have either of the 2 high molecular weight proteins in their shells: B-48 and B-100. B-48 is created in the gut and is found in chylomicrons. B-100, on the other hand, comes from the liver and is found in very-low-density lipoproteins (VLDL), VLDL remnants (IDL), low-density lipoproteins, and Lp(a) lipoproteins.

The densities of these lipoproteins are actually dictated by the amount of lipids contained in their core, in relation to the amount of protein they have in their shell. This makes chylomicrons the least dense lipoprotein among the classification, and HDLs the densest.

Lipoprotein Synthesis and Degradation

Chylomicrons
As mentioned previously, B-48, a component of chylomicrons, come from the intestines. They are responsible for the transport of dietary fats and cholesterols and travels through the thoracic duct into the bloodstream.

In under an hour, a chylomicron is eliminated in the blood by way of lipoprotein lipase (LPL) hydrolysis. LPL is found in the walls of capillaries, and other forms may include those found in the pancreas and liver. From this hydrolysis, the hydrophilic shell and hydrophobic core are taken apart. The lipids and apoproteins found in the surface are taken up by HDLs, while the rest of the chylomicron remnants are endocytosed by hepatocytes by means of a receptor-mediated process.

**VLDL**

VLDL and chylomicrons are somewhat similar in terms of metabolism (LPL hydrolysis) but differ in the way they are synthesized. VLDL is created in the liver and delivers triglycerides from there to other parts of the body.

Once they are degraded by the LPL found in the periphery, fatty acids are then produced and used for adipose storage or for fuelling ketone-dependent tissues such as the heart and other muscles. When triglycerides are removed from VLDLs, two lipoproteins come into being – VLDL remnants (IDL) which are endocytosed by hepatocytes, and LDL.

**LDL**

As already mentioned, LDL are synthesized from the triglyceride depletion of VLDLs. Popularly known as ‘bad cholesterol,’ this lipoprotein is known to carry the majority of the cholesterol in the circulation.

Once hydrolysed by LPL, free cholesterol from these lipoproteins are either used for the synthesis of cell membranes, or delivered to the liver for excretion by way of bile production. It has been found out that about 70% of LDL is eliminated from the blood with the help of the cells in the liver.

**Lp(a) Lipoprotein**

This is actually a complex formed by the covalent bonding of an (a) protein to one of the apoproteins of an LDL molecule. This lipoprotein is very much similar to plasminogen, the inactive form of the potent fibrinolytic plasmin, in structure. This has been implicated in the formation of atherosclerotic plaques attributed to coronary artery diseases by inhibiting thrombolysis.

**HDL**

The hydrophilic part of HDL, particularly the apoproteins, are produced and secreted by the liver and the intestines. However, unlike the rest of the lipoprotein classes, HDL derives its hydrophobic core from the surface monolayers of chylomicrons and LDL during lipid metabolism, and from cholesterol from the peripheries making them the ‘good cholesterol’.

Free cholesterol in the tissues and circulation are taken up by HDL and are placed further into the hydrophobic core by conversion into cholesteryl esters with the help of lecithin-cholesterol acyltransferase (LCAT). Once the molecule reaches the hepatocytes, this esterified cholesterol is released and endocytosed in exchange for triglycerides with the help of cholesteryl ester transfer protein (CTEP).
Drugs that Control Lipid Levels

Bile Acid Sequestrants

**Mechanism of Action**

Cholesterol may be excreted from the body through conversion to bile acids in the liver. This is made possible through a reaction called $7\alpha$-hydroxylation and is regulated with a negative feedback mechanism dictated by the amount of bile acids produced. Bile acids, however, are reabsorbed and recycled in the jejunum and ileum, keeping the conversion of cholesterol to bile acids somewhat at a minimum.

With the help of non-absorbable, positively-charged resins such as cholestyramine, colestipol and colesevelam, bile acids in the digestive tract are prevented from being reabsorbed in the small intestines. This, in turn, depletes the amount of usable bile acids,
forcing the 7α-hydroxylation reaction in the liver to work faster, using up more cholesterol for bile acid production. Eventually, cholesterol levels in the circulation and in tissues decrease.

**Indications**

Bile acid sequestrants are said to promote a 20% reduction in the LDL levels. However, the consequent decrease in LDL may cause an increase in VLDL in patients with hyperlipidemia. For this reason, it is used along with other medications, such as fibrates or niacin that may address this problem.

Bile acid sequestrants are commonly used for patients with:

- Primary hypercholesterolemia
- Pruritus due to cholestasis and bile salt accumulation
- Digitalis toxicity – these drugs bind digitalis glycosides

**Side Effects and Drug Interactions**

These drugs act mainly on the digestive tract and therefore cause local side effects which may include:

- Constipation
- Bloating
- Heartburn
- **Diarrhea**
- Steatorrhea