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LIPIDS OF BLOODSTREAM

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ABSTRACT

One of the important factor in the development of cardiovascular disease is hyperlipidemia, a disorder characterized by elevated lipids (fats) level in the bloodstream. Lipid is a medical term for fat found in the bloodstream. Lipids are fatty organic compounds or particles in the body that are poorly soluble in water. In view of their importance and role in human body, the composition, function and risk associated with high lipid level in the development of cardiovascular disease has presented and discussed.

KEY WORDS: Lipids, Hyperlipidemia, Cholesterol, Lipoproteins, HDL, LDL, VLDL.

INTRODUCTION

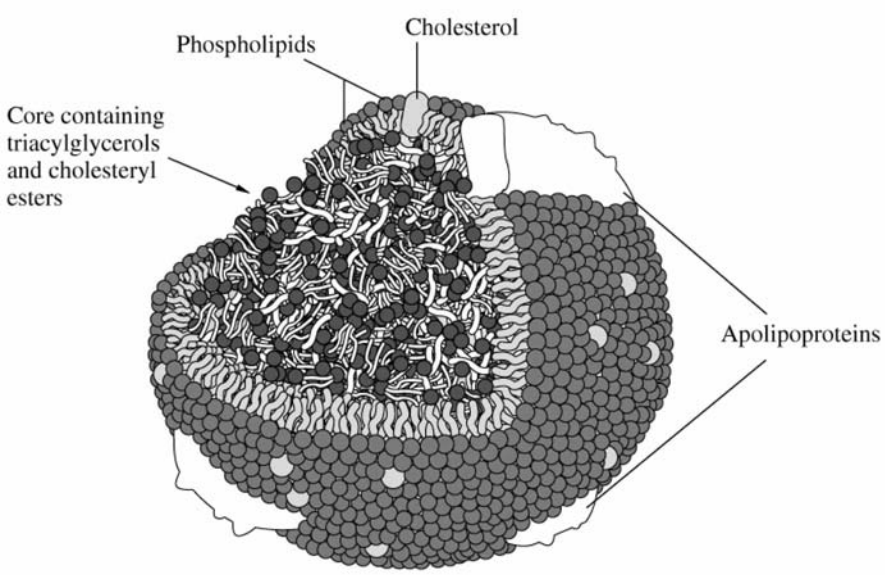
The term "lipids" describes an entire class of fats and fat-like substances in the blood. The most important lipids in the blood are fatty acids, cholesterol, cholesterol esters (cholesterol attached to a fatty acid), triglycerides (three fatty acids attached to a three-carbon glycerol), and phospholipids, such as lecithin. Fatty acids are derived from fats by hydrolysis (e.g., oleic, palmitic, or stearic acid) and are identified as esters of a long-chain monobasic organic acid. Where as triglycerides consist of glycerol esterified with three long chain fatty acid, such as stearic or palmitic acids. While phospholipids are compounds similar to the triglycerides but with one fatty acid residue replaced by phosphate and a nitrogenous base, Triglycerides are found in dietary fats, and can also be synthesized in the liver and adipose tissue to provide a source of stored energy, which can be mobilized when required, for example, during starvation. Triglycerides containing both saturated and unsaturated fatty acids are important components of cell membranes[1] .
Cholesterol and cholesterol esters are essential elements contained in all human cell membranes. Cholesterol is a structural component of steroid hormones and bile acids. It is present in dietary fats and can also be synthesized in many tissues, including liver. It is transported in the blood as part of large molecules called lipoproteins[1]. The high content of cholesterol in the body usually brings adverse impact but nevertheless it also plays some important role in the overall health and function of the body. Every cell within the body is formed to varying degrees from cholesterol. When the cholesterol level becomes elevated, it can be dangerous, however, at the appropriate level; it plays a vital role in many functions of the body. Cholesterol works to build and repair cells, produces hormones such as estrogen and testosterone, and produces bile acids proven to aid in the digestion of fats[2]. However, the high levels of cholesterol build-up in the blood can cause clogging, which in turn raises the risk for heart disease and / or stroke. Some cholesterol is produced in the body while eating saturated foods made from animal-based foods such as dairy meat, eggs, which are essential components in the elevation of cholesterol. Food such as fruits, vegetables, and grains do not contain cholesterol[3]. Cholesterol along with some other types of fats cannot be dissolved in the blood. Thus in order to be transported to and from the cells, they have to be specially carried by molecules called "Lipoproteins" (Figure – 1). These molecules consist of an outer layer of protein with an inner core of cholesterol and triglycerides[1].

Lipoproteins

Lipoproteins are macromolecular complexes that carry hydrophilic plasma lipids, particularly cholesterol and triglyceride, in the plasma. Lipoproteins are spherical particles made up of hundreds of lipid and protein molecules. They are smaller than red blood cells and visible only the electron microscopy. However, when the larger, triglyceride-rich lipoproteins are present in high concentration, plasma can appear turbid or milky to the naked eye. The major lipids of the lipoproteins are cholesterol, triglycerides, and phospholipids. A

family of proteins, the apolipoproteins, also occupies the surface of the lipoproteins; the apolipoprotein play crucial roles in the regulation of lipid transport and lipoprotein metabolisms[1]. Lipoproteins have been classified on the basis of their densities into five major classes[1,3], which include, 1.Chylomicrons., 2. Very low density lipoproteins (VLDL), 3. Intermediate density lipoproteins (IDL), 4. Low density lipoproteins (LDL) 5. High density lipoproteins (HDL). The characteristic features of the major lipoproteins classes are presented Figure-2.

FIGURE - 1
STRUCTURE OF LIPOPROTEIN



RISK FACTORS

Low density lipoproteins (LDL) carry fats to different parts of the body. It carries about 60-70 percent of the cholesterol around the body. Studies show that excess cholesterol leads to much higher risk of heart attack and / or stroke. Although there are other factors involved in this risk as age, gender, smoking, family history of heart disease, and diabetes mellitus, whereas higher cholesterol is a major contributing factor that should not be ignored[1]. High density lipoproteins (HDL), on the other hand, transport cholesterol from cells back to the liver. At this point, they are either reused or converted to bile acid and disposed. Therefore, actually helps fight the risk of heart attack and / or stroke. Because they consist of more protein than that of triglycerides or cholesterol, they work hard to remove LDL from the artery walls[1].

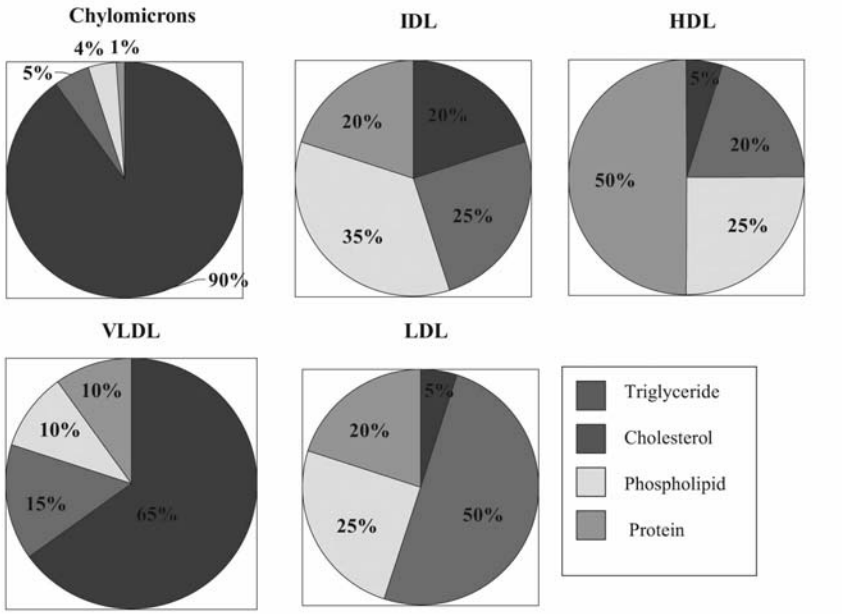
APOLIPOPROTEINS

The Apolipoproteins (Apos) provide structural stability to the lipoproteins and determine the metabolic fate of the particles upon which they reside. They were named in an arbitrary alphabetical order[4]. The characteristics of the major apolipoproteins have been summarized in Table – 1. Apo A I, apo A II, apo A IV are found primarily on HDL. Apo A I and apo A II are synthesized in the small intestine and the liver; apo IV is made only in the intestine. Apo A I comprises about 70 to 80% of the protein of HDL and plays a critical structural role in HDL particles. Individuals with a profound deficiency of apo A I also lack HDL. Apo A I activates the enzyme lecithin-cholesterol acyltransferase (LCAT), which esterifies free cholesterol in plasma. Plasma levels of HDL cholesterol and apo A I are inversely related to risk for CHD, and some patients with apo A I deficiency developed early, severe atherosclerosis. Apo A II is the second most abundant apoprotein in HDL, but its function has not been fully determined. It is proposed that apo A II is also necessary for the integrity of HDL particles. Apo A IV, a minor component of HDL and chylomicrons may play a role in the activation of LCAT.

Apoprotein (a) is a large glycoprotein that shares a high degree of sequence homology with plasminogen, is made by hepatocytes and is secreted into plasma where it forms a covalent linkage with the apo B100 of LDL to form lipoprotein (a). The physiologic role of lipoprotein (a) is not known, but elevated levels are associated with an increased risk for atherosclerosis[4]. There are two forms of apo B, apo B100 and apo B48. The apo B100 is the major apolipoprotein of VLDL, IDL, and LDL, comprising approximately 30, 60, and 95% of the protein in these lipoproteins respectively. Apo B100 has a molecular mass of about 545 kDa and is synthesized in the

FIGURE – 2

COMPOSITION OF LIPOPROTEINS



LDL = Low density lipoprotein; VLDL = Very low density lipoprotein; IDL = Intermediate density lipoprotein; HDL = High density lipoprotein.

liver. . It is essential for the assembly and secretion of VLDL from the liver and is the legend for the removal of LDL by the LDL receptor. Apo B48 is essential for the assembly and secretion of chylomicrons. Apo B48 is encoded by the same gene and messenger ribonucleic acid (mRNA) as apo B100. The role of apo B48 in the metabolism of chylomicrons in plasma is unclear; Individuals with mutations that interfere with the normal synthesis of apo B have absent or very low levels of chylomicrons, VLDL, IDL and LDL. The apolipoproteins of the C series are synthesized in the liver and are present in all plasma lipoproteins (trace amounts in LDL). Individual apo Cs have different metabolic roles, but all inhibit the removal of plasma chylomicrons and VLDL remnants by the liver[4]. Apo E is synthesized mainly in hepatocytes but is also made in other cells, including macrophages, neurons, and glial cells. It is found in chylomicrons, IDL, VLDL, and HDL and mediates the uptake of these lipoproteins in the liver by both the LDL receptors and the LDL receptor-related protein (LRP). Apo E also binds to heparin-like proteoglycan molecules on the surface of the cells. There are three major apo E alleles: E2, E3, and E4; these isoforms differ in sequence at two positions and have frequencies of about 0.12, 0.75, and 0.13, respectively, in the general population. Apo E2 binds to the LDL receptor with lower affinity than apo E3 or E4. Individuals who are homozygous for apo E2 may develop severe hyperlipidemia (type III dysbetalipoproteinemia); complete absence of apo E increases plasma levels of chylomicrons and VLDL remnants and causes early atherosclerosis[4].

Transport of exogenous and endogenous lipids

Exogenous Lipids

Exogenous lipid transport in chylomicrons and chylomicrons remnants is depicted in Figure – 3. Chylomicrons are the major transportable form of exogenous (dietary) fat. Triglyceride constitutes about ninety percent of the lipid. Triglyceride is removed from chylomicrons by the action of the enzyme lipoprotein lipase, located on the luminal surface of the capillary endothelium of adipose tissue, skeletal and cardiac muscle and lactating breast, so that free fatty acids are delivered to these tissue either to be used as energy substrate or, after re-estrification to triglyceride, for energy storage[1,4,5].

Endogenous Lipids

The endogenous lipid transport system, which conveys lipids from the liver to peripheral tissues and from peripheral tissues back to the liver, can be separated into two sub-systems: the apo B100 lipoprotein system (VLDL, IDL, LDL) and the apo AI lipoprotein system (HDL). VLDL are the principal transport form of endogenous triglyceride and initially share a similar fate to chylomicrons, triglyceride being stripped off by the action of enzyme, lipoprotein lipase (LPL). As the VLDL, particles become smaller, phospholipids, free cholesterol and lipoproteins are released from their surface and taken up by HDL, thus converting the VLDL, to denser particles, IDL. Cholesterol that has been transferred to HDL is esterified and the cholesterol ester is transferred back to IDL by cholesterol ester transfer protein in exchange for triglyceride. Further, triglyceride is removed by hepatic lipase and IDL are thereby converted to IDL, composed mainly of cholesterol ester, apo B100 and phospholipids. Some IDL are taken up by the liver via LDL receptors. Under normal circumstances, there are very few IDL in the circulation, because of their rapid removal or conversion to LDL[1,5].

TABLE – 1

CHARACTERISTICS OF THE MAJOR APOLIPOPROTEINS

Apolipo-protein	Molecular Mass, Da	Lipoproteins	Metabolic Functions
Apo AI	28,016	HDL, Chylomicrons	Structural component of HDL; LCAT activator
Apo AII	17,414	HDL, Chylomicrons	Unknown
Apo AIV	46,465	HDL, Chylomicrons	Unknown; possibly facilitates transfer of other apos between HDL and Chylomicrons.
Apo B48	264,000	Chylomicrons	Necessary for assembly and secretion of Chylomicrons from the small intestine.
Apo B100	540,000	VLDL, IDL, LDL	Necessary for assembly and secretion of VLDL from the liver; structural protein of VLDL, IDL, LDL; ligand for LDL receptor.
Apo CI	6,630	Chylomicrons, VLDL, IDL, HDL	May inhibit hepatic uptake of Chylomicrons and VLDL remnants.
Apo CII	8,900	Chylomicrons, VLDL, IDL, HDL	Activator of Lipoprotein Lipase
Apo CIII	8,800	Chylomicrons, VLDL, IDL, HDL	Inhibitor of Lipoprotein Lipase; may inhibit hepatic uptake of Chylomicrons and VLDL remnants.
Apo E	34,145	Chylomicrons, VLDL, IDL, HDL	Ligand for binding of several Lipoproteins to the LDL receptor, to LRP, and possibly to a separate hepatic apo E receptor.

HDL = High Density Lipoprotein; LACT = Lecithin cholesterol acyltransferase; VLDL = Very Low Density Lipoprotein; IDL, Intermediate Density Lipoprotein, LDL = Low Density Lipoprotein; LRP = LDL Receptor Related Protein.

Symptoms of high cholesterol

Symptoms of high cholesterol are rare, and are generally identified from blood test. The symptoms seen are actually from the end-result of high cholesterol for health issue such as Coronary disease, Stroke, and Peripheral Vascular disease[6]. The primary symptom associated with coronary heart disease is called "Angina" (chest pain). When a person experiences this, they describe a feeling of pressure, and squeezing, on their chest[6]. These symptoms can spread to the jaw, neck, or arm regions of the body and although the primary symptom is the feeling of pressure in chest region, some individuals experience that feeling of pressure in other areas and not the chest. In addition to the reported pressure, other symptoms can include nausea, shortness of breath, sweating, lightheadedness or dizziness, and heart palpitations. Angina can be directly correlated to coronary heart disease and should be taken seriously. However, there are other stress factors such as over-exertion, high-level of emotion, or even after eating a huge meal to be considered heavy. In these circumstances a short period of rest,

five minutes or so, will reduce or eliminate the symptoms. There are four primary symptoms pertaining to a stroke although often times this is a sudden event with little or no warning[7].

- The sudden onset of numbness or weakness of face, arm, or leg, especially on one side of the body.
- Confusion, difficulty in speaking or understanding.
- Sudden trouble with vision in one or both eyes.
- Dizziness, loss of balance, lack of coordination.

Other symptoms can include:

- Nausea and / or vomiting.
- Fever.
- Fainting, convulsion, and even coma.

The peripheral vascular disease (PAD) is a disease in which fatty deposit build up in the inner linings of the artery walls. In turn, arteries that carry blood to the extremities become narrow or clogged. The outcome is that the blood is slowed or stopped completely[6]. The primary symptoms of the disease are:

- Numbness and / or tingling in the lower extremities.
- A cold sensation in the lower extremities.
- Open sores or ulcers on the lower extremities that do not heal normally.

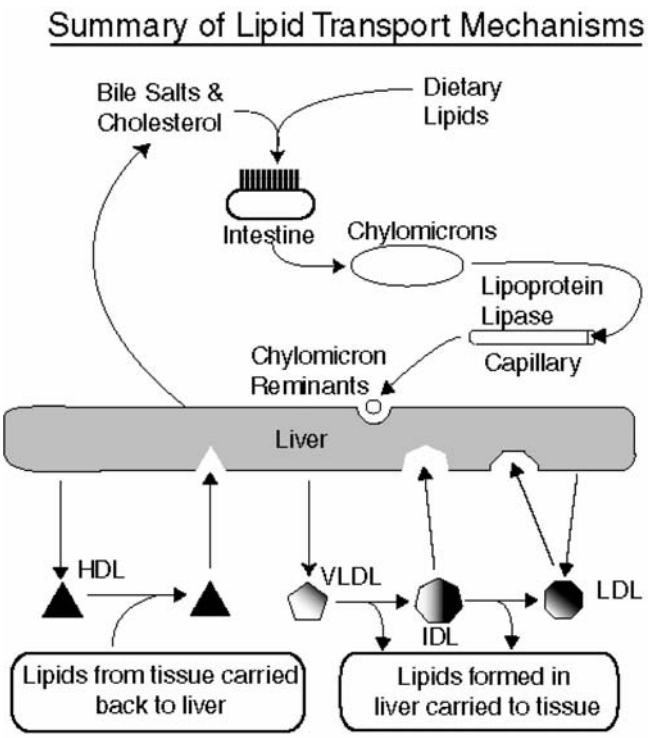
Causes of high cholesterol

Causes of high cholesterol very much depends on the lifestyle, gender or the heritage of the individual. An individual can do certain things to live healthier and prolong life. One of those choices includes maintaining cholesterol at the right level. However, the truth is even young, thin physically fit people can have high levels of cholesterol. Although chances of higher levels increase due to certain factors, such as over weight, diet containing saturated fats etc. Lifestyle management can change some of these factors while others require a more intense approach to include cholesterol lowering medications[8].

Results of the various studies reported showed that high blood cholesterol level is a risk factor for coronary heart disease (CHD). It is a general conclusion that the higher the cholesterol level, the greater the CHD risk. On the other end of the spectrum, CHD is uncommon at total cholesterol levels below 150 mg /dL. A direct link between high blood cholesterol and CHD has been confirmed by the "Lipid Research Clinics-Coronary Primary Prevention –USA" which showed that lowering total and LDL cholesterol levels significantly reduces CHD. Based on various recommendations made by the health community including the "National Cholesterol Education Program (NCEP)'s recommendations, the following chart may be used to assess the cholesterol level (Table – 1). A good rule to follow is that any total cholesterol reducing below 200 is good and anything over 240 indicates that the individual is at risk for developing coronary disease. In addition, the LDL cholesterol should measure below 130 and the HDL cholesterol should range in between 35 to 40. When HDL cholesterol, reaches 60 or higher, the individual has benefit of reducing the chance of heart attack[9,10].

FIGURE - 3

SUMMARY OF LIPID TRANSPORT MECHANISM



A – Schematic depiction of the transport of exogenously derived lipids from intestine to peripheral tissues and liver via the chylomicrons system.
B – Transport of endogenous hepatic lipids via VLDL, IDL., and LDL.

Benefits of HDL Cholesterol

Lowering LDL cholesterol is easier to do than raising HDL cholesterol. However, there is great benefit in bringing the HDL numbers up and even greater benefit by doing both – lowering LDL / raising HDL[2,3]. For a long time, focus was primarily given on LDL and the need to bring numbers down. However, researchers and physicians have now identified that bringing the HDL level up is just as beneficial and a natural way of fighting off LDL cholesterol. Although more difficult to accomplish, there are definite steps that can take to help raise the HDL:

- Weight loss
- Exercise
- Balanced diet

Communications have shown that when antioxidants are coupled with cholesterol reducing medications such as Statin-type drugs along with Niacin, there was some level of benefit. Further research suggests that in women with high plasma levels of HDL, the risk of heart attack become reduced. The higher the HDL levels, the better. Today, the average for women is between 50 and 55 mg / dL and for men 40 to 45 mg / dL. Again, getting this level over 60 is a very effective start toward improving overall cholesterol ratios. Smoking is extremely hard on the heart and overall health.

Raising HDL cholesterol was not a priority until a couple of years ago. Most studies focused on lowering LDL cholesterol that can reduce the risk or coronary heart disease.

But in the past few years, researchers have identified that HDL acted as an independent factor and was also critical in the overall health of the heart. The National Cholesterol Education Program's new guidelines now recognize that low HDL levels are a strong independent risk factor for coronary artery disease. From the research, it is known that HDL is a complex molecule made up of lipids, cholesterol, and protein. The way it works can be explained that HDL acts as much like a bottom feeder of a fish tank. It cleans off the walls of blood vessels, thus removing excess cholesterol and LDL. The LDL then carries this cholesterol to the liver where it is processed[2,3].

Physicians still focus strongly on lowering LDL but are now also recommending that raising HDL is another important factor to reduce risk of heart disease. Without a doubt, lowering LDL cholesterol is a huge benefit in bringing total cholesterol down to a safe level. There have been numerous studies conducted that indicated the chance of having a heart attack is actually decreased by as much as 25% for every 10% drop in cholesterol level. The top four benefits of lowering LDL cholesterol include:

- Decreases the chance of heart attack and / or stroke
- Reduce the formation of new cholesterol plaques
- Eliminates existing plaques
- Prevents the rupture of existing plaques.

A particular study (Scandinavian Simvastatin Survival Study, or 4S), confirmed that lowering LDL not only reduced risk for heart attacks, but death. In this study, more than 4,000 people with confirmed heart disease were given either a cholesterol lowering drug or a placebo. The drug of choice for this study was Statin. The results showed that for the people taking the Statin, exhibited that the total cholesterol levels were reduced 25%, LDL was lowered 35%, and death occurring from heart disease was reduced by a staggering 42%[8]. It is advisable to keep the daily calorie intake of fat to less than 30%. If an individual consumes too many calories from any kind of food, whether it is carbohydrates, proteins, or fats, the body will take that food and turn into triglycerides that are then circulated into the bloodstream to be stored as fat. This will simply increase the level of LDL in the blood stream, creating more risk of heart disease. If any one currently has heart disease, lowering the level of LDL will have a great impact on the health. The most encouraging news is that there are several options available to control the cholesterol level through traditional treatments, natural and herbal treatments and changing to a healthy lifestyle[8].

CONCLUSION

The important factor is to understand the risk factors by identifying the cholesterol levels and how it may affect the overall health and possible risk of a heart attack. Research has shown that every 1% reduction in cholesterol levels, there is a 2% reduction in the rate of heart disease. This should be a strong incentive in controlling the cholesterol levels. Out of several researches conducted, it is now established that many approaches are available to lower LDL cholesterol while increasing HDL to reduce the risk of heart disease.

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