Chapter

Significance of Lipid and Lipoprotein in Organism

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Abstract

Lipids are important energy and building compounds. Their decomposition provides a significant amount of energy required for various life processes. It can thus be deposited in triglycerides and adipocytes. Some of them, in conjunction with proteins, form the most important structural elements of cells and cellular organelles, while others are precursors for the synthesis of numerous active compounds such as some hormones or prostaglandins. Lipids are ingested but can also be synthesized in the body. In circulation, lipids are found packed in lipoprotein molecules because they are insoluble in water. Lipoproteins have a central lipid part (nucleus) containing triglycerides and cholesterol esters, and on the surface there is a sheath composed of certain proteins (apoproteins), phospholipids, and small amounts of free cholesterol. Thanks to this sheath, lipids can be transported via blood. It took a long time to determine the importance and role of lipids in the body, as well as their role in many metabolic disorders of various diseases. This field is still unexplored and is a challenge for many researchers to prevent and treat lipid metabolism disorders.

Keywords: lipids, lipoproteins, apolipoproteins

1. Introduction

There is evidence that Leonardo da Vinci first observed macroscopic changes in the arteries corresponding to atherosclerosis, noting that such lesions were later discovered on Egyptian mummies' aortic wall and large blood vessels. The presence of cholesterol in atherosclerotic plaque was first indicated by Vogel in 1847 [1].

An association between elevated blood cholesterol levels and atheroma was observed early this century. The credit goes to Alexander Ivanovsky, who in 1908 published a paper proving that high-energy and high-protein diets in rabbits lead to the development of atherosclerosis. Anichkov found that this resulted in increased fat infiltration into the arterial wall. The significance of this animal model was in the morphological and histochemical similarity of these changes with human atherosclerosis [2].

The landmark advances in lipidology were marked in 1985 by Michael Brown and Joseph Goldstein for the pioneering work on the role of LDL receptors, intracellular cholesterol metabolism, and its homeostasis in the body [3].

Undoubtedly of great importance for the better knowledge of the structure and metabolism of lipoprotein particles in the blood have been the great advances in the domain of learning about their protein component—apolipoprotein [4].

In recent years, hypertriglyceridemia has been found to be a risk factor for coronary artery disease and atherosclerosis [5].

From the pioneering work of Ignatovsky and Anickov at the beginning of this century, a huge journey has been made, and great discoveries have been made that have expanded our knowledge of lipid and lipoprotein metabolism to unprecedented limits [6].

2. Definition of lipids

The term lipids refers to a group of organic chemicals that are found in all animal and plant organisms.

There are several types of lipids present in the human body, the most important of which are fatty acids, cholesterol, triglycerides, and phospholipids [7].

They are an integral part of all complex lipids (cholesterol esters, triglycerides, and phospholipids) and are present in the body in the form of the so-called free fatty acids (SMK), unbound for other lipids. The 7SMKs are composed of a straight chain of carbon atoms, the number of which is, as a rule, even and the molecule ends with a carboxyl group. According to the number of carbon atoms, they are divided into fatty acids of short (up to 8 carbon atoms), medium (8–12 carbon atoms), and long chain (more than 12 carbon atoms) [8].

Based on the presence or absence of double bonds, the fatty acids are divided into saturated and unsaturated. The unsaturated fatty acids by the number of double bonds are divided into monosaturated (having only one bond) and polyunsaturated, having from two to six double bonds. They can occur in two isomeric forms, the so-called cis and trans forms [9].

2.1 Fatty acids

Fatty acids are present in the blood in two forms, either free or nonesterified (SMK, FFA) and esterified. Esterified fatty acids account for the largest part in the circulation of about 95%, while 5% of free fatty acids are found in the blood [10].

Plasma free fatty acids are reversibly bound to proteins, primarily to albumins, and to a lesser extent to globulins and lipoproteins. They are present in a very low concentration (about 0.5 mmol/l) but have an extremely fast turnover, with a half-life of 1–3 minutes. Metabolically, the most active are the plasma lipids, and their oxidation is the main source of energy in the fasting state. The esterified fatty acids are esterically bound in the composition of triglycerides (45%), cholesterol esters (15%), and phospholipids (35%) [8].

A large number of fatty acids have been discovered in nature, many of which are present in the human body. Some of the fatty acids can be created in our body, and those fatty acids that the human body is unable to synthesize must be ingested through food and are called essential fatty acids. It has already been mentioned that most of the fatty acids are in bound form, in the composition of phospholipids, triglycerides, and cholesterol esters, and only 5% of free fatty acids are in free or unbound form (free fatty acids). It should be borne in mind that many properties of triglycerides, cholesterol, and phospholipids depend significantly on the type of fatty acids that make up their composition. It is also of great importance whether the fats in the diet are dominated by saturated, monounsaturated, or polyunsaturated fatty acids [11].

Cholesterol is best known among lipid fractions and plays the most important role in the formation of atherosclerosis. It is a special type of lipid, which differs significantly from other lipid substances in its chemical structure. In pure form, the whitish soft waxy substance is insoluble in water [11]. It is present in the body in free, nonesterified, and esterified form bound to a single fatty acid in the form of cholesterol esters [12].

Cholesterol esterification occurs in the plasma under the action of the enzyme lecithin-cholesterol acyltransferase (LCAT). Plasma contains about 75% of the cholesterol in the esterified state and most often esterifies with polyunsaturated linoleic fatty acid about 55% [13].

Most of the free (nonsterified) cholesterol is found in tissues. Cholesterol is a necessary component of the body. It is a structural element of all cellular and intracellular membranes and has specific roles in specific organs (e.g., in hepatocytes where it participates in the synthesis of bile acids, in the cortex, and in the synthesis of steroid hormones, and it plays the role of transporters of liposoluble vitamins A, D, E, and K).

The origin of cholesterol in the body is twofold (endogenous and exogenous). Most cells have the ability to synthesize it themselves, and its other source is the food it feeds on. It has been found that 2/3 of cholesterol is produced by synthesis in the body (in adults about 800–900 mg/day) and only 1/3 is ingested by food. Considering the ability of the organism to produce it in large quantities, it is quite sufficient to feed 150–300 mg daily with food. Excess cholesterol from the body is eliminated through the bile (by conversion to bile acids) and by skin peeling, and a very small amount is lost by urine. Breastfeeding women also lose some cholesterol through milk. From all of the above, it is obvious that cholesterol is essential to the body and is of great importance for the normal functioning of each cell. Its adverse effects are manifested when it is present in much higher concentrations in the blood [14].

2.2 Triglycerides

Triglycerides are esters of glycerol, a trihydroxy alcohol with fatty acids. It is possible to esterify only one, two, or all three hydroxyl groups of fatty acid glycerol to produce mono-, di-, or triglycerides. Triglycerides are most prevalent in the body, while diglycerides, and especially monoglycerides, are present in significant amounts only in the intestinal mucosa during fat absorption [12].

Their basic role in the body is the creation of energy depots from which, when necessary, they release fatty acids, whose oxidation provides the energy necessary for the life of all cells. The highest amount of triglyceride is found in the composition of adipose tissue (about 95%), while insignificant amounts are present in the blood. Triglycerides have also been reliably found today to have an increased amount in the blood in the process of atherosclerosis [15].

2.3 Phospholipids

The chemical structure of phospholipids is very complex. It is an ester-bound two-fatty acid molecule for one alcohol, which contains phosphoric acid as an integral part of its molecule. Depending on the alcohol they contain, they are divided into two groups, glycerophospholipids (containing glycerol) and sphingophospholipids (containing sphingosine). With the exception of fatty tissue dominated by triglycerides, phospholipids are the basic lipids of cell membranes and other cellular structural elements. It should be emphasized that the brain and nerve tissue are the richest in phospholipids [7].

3. Definition of lipoproteins

An important feature of lipids is their insolubility in water. In order to dissolve it in the blood and transport it to all cells of the body, all lipid substances are bound to certain proteins, thus forming particles called lipoproteins [8].

The lipid part of the lipoprotein particles consists of cholesterol, cholesterol esters, triglycerides, and phospholipids, and their protein parts are very different in structure and are called apolipoproteins. Depending on the type and amount of lipids, on the one hand, and the amount and type of protein part, or apolipoprotein, on the other, different types of lipoproteins are present in the blood [4].

The four basic types of lipoprotein particles present in the blood of all persons are chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) (**Table 1**) [7].

Today, the labeling of lipoprotein particles with abbreviations deriving from English names, i.e., as VLDL, LDL, and HDL particles, is accepted worldwide. They should also be supplemented with chylomicrons, which have the largest circulating lipoprotein particle [7].

Certain lipids (cholesterol, triglycerides, phospholipids) are found in the blood in the composition of all lipoprotein particles, in different amounts, and in combination with other constituents of lipoprotein particles. Chylomicrons and VLDLs contain predominantly triglycerides, LDL mainly cholesterol, while HDL particles are most abundant in the protein moiety and lipids in phospholipids. One person's blood cholesterol represents the sum of cholesterol present in all lipoprotein particles, in chylomicrons, VLDL, LDL, and HDL, although its largest amount (about 70%) is found in LDL particles. Depending on the physiological role of individual lipoprotein particles, the increase in cholesterol in one of them will have a different significance for the organism. Cholesterol contained in the LDL particle leads to atherosclerosis, while the increase in cholesterol in HDL particles has a protective effect against atherosclerosis [6]. In addition to chylomicrons, VLDL, LDL, and HDL particles, some other types of lipoproteins are normally present in the blood. Among these lipoprotein species is the so-called lipoprotein Lp(a). It is a special type of lipoprotein, which has been shown to be present in the blood of every person at quite minimal concentrations (up to 0.25 g/l). Lipoprotein Lp(a) together with the LDL particle represents the most serious lipid risk factor for atherosclerosis [7].

3.1 Apolipoproteins

Lipids are mostly insoluble in water. In plasma, they can be in the form of stable complexes if they are attached to specific protein moieties called apolipoproteins or apoproteins (Apo).

The protein part of the lipoprotein particle was previously thought to be a lipid transport agent only. However, they have been found to have other, very significant roles in the body. Apoproteins provide stability of plasma lipid transport. They are cofactors of individual enzymes that participate in the metabolism of lipoprotein particles. Their most important function is to bind to specific receptors on cell membranes, thereby ensuring the entry of plasma lipoprotein particles into cells and their further catabolism [2, 15, 16].

• Hilomicrones
• Very low-density lipoproteins (VLDL) Pre-beta-lipoproteins
• Low-density lipoproteins (LDL) Beta-lipoproteins
• High-density lipoproteins (HDL) Alpha-lipoproteins

Table 1.
Basic blood lipoprotein particles.

The structure and concentration of individual apolipoproteins in a particular lipoprotein particle are under a direct genetic control, as opposed to serum lipid content, which is significantly more influenced by diet and metabolism [17].

3.1.1 Apolipoprotein A-I

Apolipoprotein A-I (Apo A-I) is the major apolipoprotein of HDL particles. About 90% of Apo A-I is in HDL fractions. In the HDL particle alone, it accounts for 65% of the total protein portion. It is present in small amounts in the chylomicrons and the VLDL fraction. It is synthesized in the liver and small intestine wall. Its most important role is the activator of the enzyme LCAT, which allows esterification of free cholesterol on the surface of HDL particles. In this way, small discoidal HDL3 particles accept excess cholesterol from the cells and accumulate it in the form of esterified cholesterol, thereby transforming it into larger, more soluble, lower-density HDL2 particles. Since it allows the uptake of free cholesterol and subsequently its esterification, it is logical that it has a protective effect on the process of atherosclerosis [18].

3.1.2 Apolipoprotein A-II

Apolipoprotein A-II (Apo A-II) represents about 20–30% of total HDL particle proteins. It forms in the liver and the small intestine wall. It is thought to have an inhibitory effect on LCAT and modulatory effect on the activity of lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) [19].

3.1.3 Apolipoprotein B

Apolipoprotein B (Apo B) is present in the human population in two forms, as apolipoprotein B-48 (Apo B-48) and apolipoprotein B-100 (Apo B-100).

Apo B-48, which is part of the chylomicron, is synthesized in the small intestinal wall. Far more significant is Apo B-100, which is synthesized predominantly in the liver, and is a constituent of VLDL, the intermediate-density lipoprotein (IDL) that circulates for a short time, LDL particles, and the lipoprotein Lp(a). This apoprotein is also characterized by containing certain amounts of carbohydrates (approximately 5% of the total mass), which is chemically classified as glycoproteins [20, 21].

Apo B-100 is secreted primarily from the liver in the form of VLDL particles. By further metabolizing VLDL via IDL, LDL particles are formed that contain exclusively Apo B-100 [4]. The most important role of Apo B-100 is to specifically bind LDL particles to cellular receptors in the liver and other tissues [22].

Given that Apo B-100 is the only apolipoprotein in LDL particles known to have the most heterogeneous effect, it is understandable that an increase in plasma Apo B-100 concentration increases atherogenic risk. Due to the fact that only one Apo B-100 molecule is present in the LDL particle, unlike the amount of cholesterol that can vary in them, the plasma concentration of Apo B-100 is a better indicator of the content of atherogenic lipoprotein particles in the blood than the determination of LDL cholesterol [23].

3.1.4 Apolipoprotein C

The apolipoprotein C (Apo C) group is represented by three different proteins that are synthesized in the liver [20]. There are chylomicrons, VLDLs, and newly formed HDL particles bound in the circulation. During intravascular metabolism of lipoprotein particles, there is an intense exchange of Apo C. From HDL particles,

these apolipoproteins transfer to lipoprotein particles rich in triglycerides, namely, chylomicrons and VLDL. Apparently, Apo C plays a significant role in the catabolism of triglyceride-rich lipoproteins [24].

3.1.5 Apolipoprotein E

Apolipoprotein E (Apo E) is a protein molecule composed of 229 amino acids, which contains 10% of the amino acid arginine, and is therefore called the "arginine-rich protein" [16]. The main site of its synthesis is the liver, but it is also created in other organs: brain, spleen, lungs, adrenal gland, kidneys, ovaries, muscles. It plays a significant role in the metabolism of various lipoprotein particles: chylomicrons, VLDL, IDL, and HDL containing Apo E.

Apolipoprotein E participates in the reversible transport of excess cholesterol from peripheral tissues into the liver via HDL particles, which when incorporated into cholesterol incorporate Apo E [25].

Apo E also appears to be involved in reparative responses to tissue damage. An increase in its concentration is found in sites of peripheral nerve damage and regeneration [25]. It has significance in nerve regeneration, growth, and/or differentiation of neurons [26].

3.1.6 Apolipoprotein (a)

Apolipoprotein (Apo A) is a relatively large molecular weight protein that is incorporated into the lipoprotein composition of Lp(a).

If Apo A is isolated, the rest of Lp(a) in its composition is almost identical to the LDL particle because it has a similar lipid composition and contains a single molecule of Apo B-100. The gene that regulates the synthesis of this apolipoprotein is located on the sixth chromosome near the plasminogen gene. Apo A has a great structural similarity and shows immune cross-reactivity with plasminogen, which could be a link between atherosclerosis and fibrinolysis [27].

4. Conclusion

Lipid disorders are of fundamental importance for atherogenesis and even the occurrence of ischemic heart disease and other cardiovascular and cerebrovascular diseases. They are often associated with diabetes, obesity, and hypertension with which they interact synergistically, leading to arteriosclerotic changes. Atherosclerosis is caused by changes in the wall of blood vessels characterized by lipid deposition and cell proliferation. Deposited lipids in the blood vessel wall originate from plasma lipoproteins, and elevated cholesterol, especially LDL cholesterol, is a major risk factor. Atherogenic lipoproteins include, in addition to LDL particles, almost all classes of Apo B-containing lipoproteins (VLDL, VLDL residues, IDL, Lp(a), and oxidized LDL). A common feature of all atherogenic lipoproteins is that they contain different amounts of cholesterol esters and/or Apo B-100 or Apo B-48. Atherogenic effects of triglyceride-rich lipoproteins are associated with postprandial lipemia after fatty meal intake. Atherosclerosis is considered an inevitable process at the present stage of medical science development. In most people, around the age of 85, it is thought that about 60% of coronary circulation is covered by atherosclerotic plaques, provided that no risk factors are present during life. In the presence of risk factors such as hypercholesterolemia, such changes in the coronary vessels are reached sometime in the 42nd year of life. This early atherosclerosis is a global problem for humanity today. The major risk factors for

cardiovascular disease are the values of total LDL and HDL cholesterol. Higher HDL cholesterol has also been shown to have a protective effect. Elevated triglyceride levels also increase the incidence of myocardial infarction, even when HDL cholesterol levels are normal. Based on the studies, it was concluded that the level of total cholesterol was important in the assessment of total individual risk but the value of LDL cholesterol was taken as the goal of therapy for lipid abnormalities.

Conflict of interest

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