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The Importance of Modified Lipoproteins in Diabetes Mellitus

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ABSTRACT

The dramatic nature and relevant problems of diabetes are defined by the prevalence of Type 1 diabetes, the high mortality and an early disability in patients. The prevalence of diabetes in western countries makes up 2-5% of the population, while in developing ones it reaches up to 10-15%. Diabetes is the leading cause of cardiovascular diseases, blindness, chronic kidney failure that promotes the development of atherosclerosis. The author has analysed papers on this subject where the early signs of artherosclerotic lesions are seen at the cellular level in a vascular wall. Atherosclerosis develops rapidly in patients with diabetes. That is the deposition of lipids, mainly, cholesterol and its esters. The deposition sources are mainly lipoproteins of low density. Atherogenic properties of blood serum in patients with diabetes are caused by the modification, i.e. changes in apoprotein (V-100). The main sign in diabetes mellitus is hyperglycemia that leads to increase the maintenance of a non-enzymatic glycosylation, which represents a complex of consecutive mechanisms of the modified lipoproteins leading to the emergence. Thus, LDLlose affinity to the receptors on peripheral cells and they are inevitably collected in the blood stream, promoting the development of atherosclerosis.

KEYWORDS

Atherosclerosis, Low-density lipoprotein, Diabetic Angiopathies, Glycation, Foam cells

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder that is characterised by abnormally high glucose level in blood (hyperglycemia) because the body is not able to produce enough insulin to fill its needs. Insulin is a hormone of pancreas that is released to control the amount of the glucose, entering to the bloodstream.

Type 1 diabetes (T1D) is generally considered to be an autoimmune disorder. For unknown reasons, the immune system destroys the insulin producing β-cells of the islets of Langerhans in the pancreas in people with T1D. The damage of these cells impairs insulin production and leads to the classic signs and symptoms of T1D, namely, polyuria (production of abnormally large volumes of dilute urine), polydipsia (abnormally great thirst), polyphagia (increased appetite) and unexplained body weight loss [1]. The other symptoms may include nausea, peripheral neuropathy, fatigue and blurred vision etc. It can occur at any age, most often it starts in adolescence. It can also affect children. It's partly inherited, with multiple genes, including certain HLA genotypes, known to lead to the risk of diabetes. The complications of DM may include the following: 1) nerve damage (neuropathy); 2) kidney failure (nephropathy); 3) eye damage (retinopathy); and foot damage that may lead to gangrene and leg amputation.

T1D occurs in 10 to 20 per 100,000 people per year in the United States. By the age of 18, approximately 1 in 300 people in the United States develop T1D. The disorder occurs with similar frequencies in Europe, UK, Canada, and New Zealand. It occurs much less frequently in Asia and South America, with reported incidences as low as 1 in 1 million per year. For unknown reasons, the incidence of T1D has been increasing by 2 to 5 % each year during the past 20 years worldwide. It accounts for 5 to 10 % cases of diabetes worldwide. Diabetes is said to become the seventh leading cause of death by 2030 as it is predicted by the WHO [2].

MAIN BODY

Atherosclerosis is one of the main and independent risk factors of DM. Cardiovascular disease is found in more than 65% of patients with DM, it is the basic cause of the mortality in DM. The main hazards that arise in diabetic patients are the late complications. The late complications involve a number of clinical syndromes that are mainly associated with the damage of a vascular wall of large and small arteries. It is assumed that the cause of large vessels lesion are the atherosclerotic processes, despite the fact that some pathological changes are specific to diabetes. It was found, that premature development of atherosclerosis and accelerated progression is the feature of diabetes [3]. Nevertheless, the mechanisms of accelerated

atherogenesis in diabetes remain unclear. The typical features of early atherosclerotic lesions at the cellular level in a vessel wall are the deposition of lipids within the cells, mainly cholesterol and its esters. It is believed, that the sources of accumulating lipids, mainly, are low-density lipoproteins (LDL). At the same time, the manifestation of atherogenic effect requires a chemical modification of lipoprotein particles. Lately, the presence of the modified LDL in blood in various diseases, including diabetes, has been confirmed in the experiments. Although, the clinical significance of the identified modified changes are still unknown [4].

What is a modified lipoprotein?

Some of these lipoproteins will be discussed below, namely, Lipoprotein (a) (also called LPAor LPA), glycated LDL, oxidised LDL, and, particularly, small dense LDL particles and their role in the development of atherosclerosis.

LPA is one of the most important modified LDL, which differs from the normal LDL, as its apolipoprotein B-100 is attached through a disulfide bridge to a polypeptide chain. Apo (a) is very similar to the protein plasminogen. LPA represents spherical particles floating in the density of range between LDL and HDL (1,050-1,085 g / ml). The average particle diameter ranges between 21, 0-26, 5 nm. It contains 27% protein, 65% lipid (cholesterol ester-59%, free cholesterol and phospholipids- 14%) and 8% carbohydrate. The half-life of LPA is an average of 3.3 days, i.e. it runs for a long time in the bloodstream, it undergoes oxidation and adheres to endothelial cells, causing inflammation foci adhesion damaging the endothelial cells and paves the way for LDL in the arterial wall, with subsequent formation of an atherosclerotic plaque. Elevated levels of LPA are not reduced when receiving conventional lipid-lowering drugs (statins). LPA contributes to atherosclerosis, because it is easily oxidized and absorbed by the macrophages, and it has antithrombotic activity. Other effects of LPA are increased deposition of LDL in an arterial wall, foam cell formation, production of oxygen free radicals, monocytes, smooth muscle cell proliferation and chemotaxis of monocytes to endothelial cells [5, 6].

Oxidised LDL

With the increased formation of free radicals (hyperglycemia, hyperhomocysteinemia etc.) occurs the oxidation of LDL lipid membranes and the introduction of these products of lipid per oxidation, particularly, malondialdehyde. This process disturbs the usual affinity of LDL to its receptors and simultaneously increases the rate of absorption of oxidised LDL by macrophages, the formation of foam cells that are the initiators of the development of atherosclerotic plaque [6].

Glycated LDL

Non-enzymatic attachment of glucose to lipoproteins of different density, especially LDL also alters its structure and their affinity to relevant receptors on the surface of the peripheral cells. As a result, glycated lipoproteins, trapped in the bloodstream, are subjected to oxidation and deposited in the arterial wall, captured by macrophages, and runs a chain of processes of atherogenesis. The endothelial cells, especially their proteins receptors, as LP may be subjected to the subsequent formation of advanced glycation and results in the formation of the end products of glycation [7]. Consequently, endothelial cells express a number of receptors for the formation of the end products of glycation. Further, there is an induction of cell adhesion molecules that attract macrophages, increasing the allocation of tissue factor, cytokines and other active proteins. All this stimulates the vascular inflammation, migration of macrophages and cholesterol, especially LDL, modified in the focus of inflammation (walls of the arteries). Thus, endothelial dysfunction and diabetes-mediated atherosclerosis is developing [8].

Small dense LDL

Another important group of modified atherogenic lipoproteins are called small dense LDL. Endothelial cells, especially their proteins receptor, like as LP may be subjected to the subsequent formation of advanced glycation and results in the formation of the end products of glycation. High level of small dense LDL plasma is associated with a high risk of cardiovascular disease. There are several differences between the particles of usual LDL: small dense LDL contains less free cholesterol and phospholipids on their surface than large LDL. These differences in the lipid composition determine proper conformation of apolipoprotein B-100, making it more attractive for proteoglycan-binding sites on the endothelial cells [8].

In diabetes, there is a wrong lipoprotein metabolism.

A very low-density lipoprotein (VLDL) releases from the liver and isolates into the bloodstream. Then this LDL in the capillaries of the peripheral tissues is exposed to an enzyme called lipoprotein lipase. This enzyme acts on the LDL particles, thereby turning them into the intermediate LDL. This conversion also produces free fatty acids, which falls directly into the blood from the body tissue. At the same time the remnants of the LDL, i.e. intermediate density lipoproteins (IDL), circulates back to the liver. At this time, the hepatic lipase acts on these particles in the liver, this leads to the formation of fatty acids and LDL.

The triglycerides in the form of lipoprotein are able to penetrate into the hepatocytes of the liver through large open pores, and where in the LDL remain Apo B-100 protein, and which further determines, mainly the nature of LDL [9]. Then the LDL reacts with the receptors of low-density lipoprotein on the peripheral cells and is absorbed by the liver cells and other cells which are fully recyclable. The pathological changes associated with the development of atherosclerotic lesions occur in the intimae of large arteries and, above all, affect the cells of the intimae and smooth muscle cells. The primary cell cultures of human aortic intimae can be used for the study of development of early atherosclerotic lesions at the cellular level. Thus, there was found the accumulation of cholesterol in the cultured cells in the blood serum and the LDL in patients with atherosclerosis. In addition, it was found that the serum of patients with diabetes also causes the accumulation of intracellular lipids, i.e. it has atherogenic properties. Atherogenic serum detection is seen in 55% of cases of T1D and in 90% of cases - in T2D. In this case, lipoprotein-deficient serum (devoid of all lipid-containing particles) completely lost atherogenic potential, and from all classes of lipoproteins only LDL caused the accumulation of cholesterol in the cells [10].

Thus, the atherogenic properties of the blood serum of patients with diabetes are caused by low-density lipoproteins. These data were also an indication of the existence of modified LDL in diabetes, as native LDL in healthy individuals did not cause the accumulation of intracellular lipids. The most probable mechanism of modification of LDL in DM is non-enzymatic glycosylation of proteins (particularly Apo B100) [11]. This process is a complex sequence of chemical reactions leading to the formation of stable covalent bonds between the molecules of glucose and free

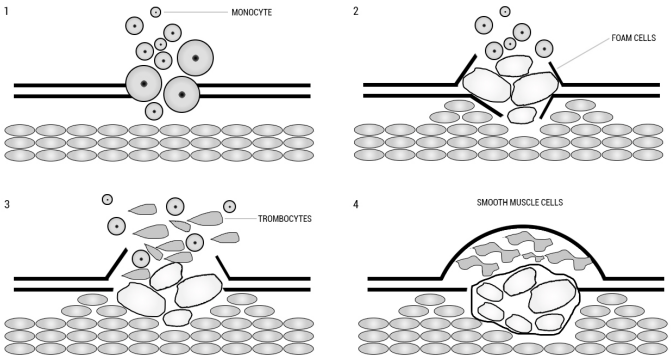

Figure 1.Formation of atherosclerotic plaques

amino groups of the protein. In diabetes, hyperglycemia leads to an increase in non-enzymatic glycosylation content of products, which also manifests itself an elevated level of LDL fructosyllysine in patients with diabetes [12].

Glycosylation of lipoproteins

In diabetes, LDL are normally exposed to high levels of glucose. From this impact LDL become glycosylated (glycated). Wherein the glucose molecule is bound to them through the free amino group (-NH2), and thus are formed glycated low-density lipoproteins. The process of glycation is not only occured in the intimae, but also in the blood plasma. As a result, the catabolism of LDL slows and develops hyperlipoproteinemia and hypercholesterolemia. In contrast, high-density lipoprotein glycation (HDL) leads to an acceleration of their catabolism and develops hypolipoproteinaemia [13]. The end products of glycosylation of lipoproteins contribute to atherosclerosis: they increase endothelial permeability thus increasing the interendothelial gaps to promote adhesion of vascular endothelium; they activate the processes of attracting monocytes and macrophages in the arterial wall, as well as the proliferation of smooth muscle cells [14]. Intimal infiltration of circulating leukocytes and monocytes, which are transformed into macrophages and capturing modified LDL, are transformed into foam cells (Figure 1).

Prior to the interaction of monocytes and T-lymphocytes with the endothelial cells and their penetration into the sub endothelial spaces, there occurs the adhesion of these cells to the endothelium. This process involves specialised adhesive molecules and some cytokines. The migration of leukocytes into the sub endothelial space is not only influenced by the chemo attractant cytokines and also due to

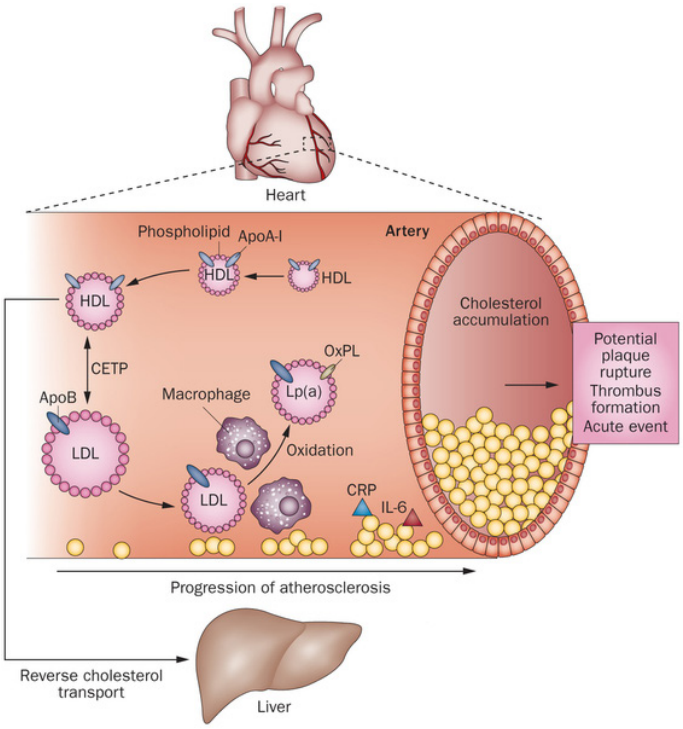

Figure 2.The scheme of accumulation of LDL in the walls of the arteries

the participation of modified LDL. Loaded with the lipids, macrophages are involved in the removal of lipoproteins accumulated in the hearth of developing atherosclerotic lesions. But in hyperlipidemia and in a significant accumulation of lipids in the arterial wall macrophages, this function is broken [15]. As a result, foam cells, i.e. macrophages overloaded with lipids, most of them remain in the intimae of arteries and die while undergoing apoptosis. As a result of glycosylation lipoproteins acquire the ability to cause accumulation of cholesterol esters in cultured monocyte-macrophages of an organism. The same effect of glycosylation of LDL is found in the cell culture of human aortic intimae. Glycosylation accompanied by equimolar LDL lowers the contents of free amino groups, as glucose reacts primarily on lysine amino groups to form Schiff bases [16].

It is believed that the free lysine residues play an important role in determining the tertiary structure of apolipoprotein B, and a decrease in their number could seriously disrupt cellular metabolism of glycated LDL. Indeed, as a result of non-enzymatic glycation ,it decreases the affinity to the classic LDL receptor and increases the grip of LDL by macrophages and slows the clearance of LDL in blood plasma, thus increasing the covalent binding of LDL to the components of the connective tissue in the matrix of the vessel wall and there are generated free radicals that are involved in oxidative damage to the protein and lipid components

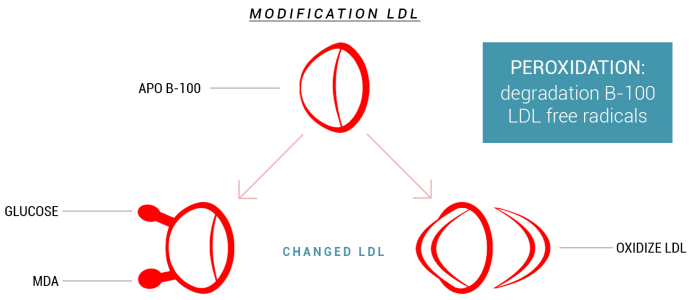

Figure 3.Formation of the modified LDL under the influence of glucose and low-new aldehyde (HMM)

of lipoprotein particles i.e. small dense LDL particles are bound badly with the receptor s of LDL in the liver [17, 18]. Small dense LDL particles, which are formed in the blood stream under the influence of some factors such as macrophage-associating phospholipase A2 affect the coronary artery. LDL affects on the endothelial wall of the coronary artery. They can easily penetrate through the barrier into the sub endothelial space. This is because the small, dense LDL particles have a higher permeability through the endothelial wall [19]. As micro LDL have no affinity for receptors as large LDL, they are not metabolised, accumulated, oxidised but promotes the formation of atherosclerotic plaques (Figure 2).

In recent years, there is an evidence that non-enzymatic glycation is not the only mechanism of artherogenic modification of LDL in diabetes.

Apparently, in human blood in diabetic patients occurs multiple modifications of LDL, i.e. - The complex process, including disyllation of proteinaceous and lipid component of LDL, the reduction in the number of neutral lipids, the reduction in the size of lipoprotein particles and thus increase in their density increases the negative surface charge [20, 21]. The modification of free amino groups, the change in the tertiary structure of apoprotein and accumulation of the lipid products by per oxidation under these conditions non-enzymatic glycation should be considered as an additional factor contributing to the enhanced modification of LDL, which may explain the biochemical features of accelerated atherogenesis in DM (Figure 3).

CONCLUSION

Modern data in respect of the role of multidrug-modified LDL in the cellular mechanisms of atherogenesis allow us to estimate the need of effective glucose-lowering therapy in diabetes.

In fact, the achievement of stable and continuous compensation of carbohydrate metabolism limits non-enzymatic glycosylation processes and thus substantially eliminates the atherogenic mechanism for modifying LDL [22]. Unfortunately, to date, there are no significant evidences that a clear metabolic regulation in any degree prevents the accelerated development of atherosclerosis in DM.

Thus, the conclusion follows that there is an urgent need of research in clinical laboratories for the formation and fate of modified lipoproteins and their main components - cholesterol and apolipoproteins. Modern medical science has a lot of information on these issues. Of course, the new information about them will be constantly growing and growing. Atherosclerosis - a very complex pathology. It simply cannot defeat a main trouble ofmankind. The widespread laboratory practice determines the first total blood cholesterol, HDL cholesterol further, and then the difference between these values to give the level of LDL cholesterol. It cannot give the clinician the ability to identify accurately the atherogenic risk associated with disturbed metabolism of lipoproteins.

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