DYSFUNCTIONAL HIGH DENSITY LIPOPROTEINS IN TYPE 2 DIABETES

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ABSTRACT

The risk of developing cardiovascular diseases (CVD) in people with type 2 diabetes mellitus (T2DM) increases by 2–4 times. One of the major factors increasing cardiovascular risk is dyslipidemia, which involves abnormalities in all lipoproteins, including high-density lipoprotein (HDL). The development of T2DM is accompanied not only by a decrease in HDL levels, but also by significant changes in their structure. This leads to the transformation of native HDL into so-called dysfunctional, or diabetic, HDL, which lose their antiatherogenic, cardioprotective, anti-inflammatory and antidiabetic properties. In poorly controlled diabetes, HDL can not only lose its beneficial functions, but also acquire pro-atherogenic and pro-inflammatory functions. Diabetic HDL may contribute to the development of adverse processes such as increased proliferation, migration and invasion of cancer cells. Considering that HDL, in addition to participating in cholesterol transport, perform important regulatory functions in the body, there is reason to assume that structural modifications of HDL (oxidation, glycation, enrichment with triglycerides, loss of HDL-associated enzymes, etc.) are one of the reasons for the development of vascular complications diabetes

Keywords: high density lipoproteins; diabetes mellitus type 2; structure modification; dysfunction; review.

INTRODUCTION

The total number of patients with diabetes mellitus (DM) in the Russian Federation as of January 2021 was 4,799,552 (3.23% of the Russian population), of which the share of type 2 DM was 92.5% (4.43 million). The main cause of high mortality in diabetes is cardiovascular diseases (CVD) [1]. The development of CVD in people with type 2 diabetes (T2DM) increases 2–4 times [2]. One of the major contributors to increased cardiovascular risk associated with diabetes is dyslipidemia, which involves abnormalities in all lipoprotein fractions, including high-density lipoprotein (HDL) [3]. Dyslipidemia develops in 72–85% of patients; changes in the lipid spectrum often precede the development of T2DM by several years [4]. Large epidemiological studies have demonstrated an inverse association between serum HDL-cholesterol (HDL-C) concentrations and the risk of coronary heart disease (CHD). Each increase in HDL cholesterol by 0.026 mmol/l reduces the risk of developing coronary artery disease by 2–3% [5, 6]. Patients with low HDL levels are 2 times more likely to suffer from diabetes and have a higher risk of developing associated cardiovascular complications, peripheral neuropathy and diabetic nephropathy [7, 8]. HDL counteracts metabolic disorders associated with T2DM. They have potential antidiabetic properties, which is confirmed by experimental studies: HDL increases glucose uptake by skeletal muscles and stimulates the synthesis and secretion of insulin by isolated islets of Langerhans of the pancreas [9, 10]; inhibit β-cell apoptosis [8, 10]; increase the sensitivity of peripheral tissues to insulin [11]. Administration of human apoA-I to insulin-resistant mice resulted in significant improvement in insulin secretion and stimulation of glucose uptake in skeletal muscle [12, 13]. This therapeutic potential was confirmed in a study in patients with T2DM [11]. In addition to the direct effect on glucose metabolism, HDL affects the reverse transport of cholesterol from the arterial wall and peripheral tissues to the liver; protect low-density lipoproteins (LDL) from oxidation; have anti-inflammatory and vasodilating effects on the cells of the vascular wall [6, 8]. Currently, there is a growing body of evidence indicating that modified HDL is impaired in its ability to reverse cholesterol transport and loses its atheroprotective properties [8, 14]. Moreover, in poorly controlled T2DM, HDL may lose its beneficial functions and acquire proatherogenic, proinflammatory properties. Such HDL is usually called dysfunctional, and in the case of diabetes, diabetic HDL [6, 8, 15, 16]. 1. Violation of the structure of HDL in T2DM Patients with T2DM experience quantitative changes in the spectrum of lipoproteins: the level of HDL, HDL-C and apolipoprotein A-I (apoA-I) decreases, the concentration of apoB (the main protein of LDL and very low-density lipoproteins (VLDL) increases)). The highest levels of apoB, atherogenic index were noted in the group of patients with high levels of triacylglycerides (TAG) in the blood serum. In 80% of patients with T2DM, HDL is

enriched in TAG, the content of which in HDL can reach 2.6 mmol/l [3, 17]. The lowest HDL-C levels were observed in individuals with poorly controlled T2DM and high levels of glycated hemoglobin (HbA1c) [18]. Low HDL-C levels are the most common abnormality observed in men with T2DM [19]. HDL particles in T2DM undergo qualitative changes, including enrichment of TAG, depletion of cholesterol esters, conformational changes of apoA-I, glycation or oxidative modification of apolipoproteins, lipids and/or HDL-associated enzymes. The replacement of cholesterol esters with TAG in the lipid core of HDL leads to a decrease in the penetration of the central and C-terminal regions of apoA-1 into the lipid phase, increasing the availability of amino acid residues, in particular methionine, for lipid peroxides. The loss of cholesterol esters leads to the loss of conformational stability of apoA-I and the formation of unstable particles, which are more quickly removed from the blood circulation. It is assumed that the ratio of cholesterol/TAG esters in HDL is a key factor determining their residence time in the blood [20]. Since diabetes is associated with long-term chronic inflammation, in patients with T2DM, apoA-I is replaced by the pro-inflammatory acute phase protein SAA (Serum Amyloid A), which is transported in small fractions of HDL and easily displaces apoA-I and other apolipoproteins from the surface of particles (up to 86% of total HDL protein). Replacing apoA-I with SAA promotes accelerated removal of HDL from the circulation and increases the binding of HDL to proteoglycans of the arterial wall [21]. In patients with T2DM, the content of apoE in HDL is reduced, which impairs the outflow of cholesterol from human macrophages to HDL and increases the binding of LDL to the vessel wall.

CONCLUSION

The results of numerous studies indicate that the development of T2DM is accompanied not only by a decrease in the level of HDL in the blood plasma, but also by significant changes in their structure. These changes lead to the transformation of native HDL into so-called dysfunctional or diabetic HDL, which lose their ability to perform antiatherogenic, cardioprotective and anti-inflammatory functions. Modifications of HDL in T2DM such as glycation, oxidation, depletion of cholesterol esters and accumulation of TAG, decreased activity of the enzymes PON-1, PAF-AH, LCAT, replacement of apoA-1 with SAA not only worsen their functions, but also contribute to the acquisition of pro-inflammatory, pro-atherogenic properties, enhance tumor metastasis. It is possible that certain drugs (BPEX inhibitors or SR-B1 inhibitors) not only increase HDL and HDL-C levels but may cause dysfunctional HDL cholesterol in patients with diabetes. For example, the lipid-lowering drug torcetrapib increases the content of apoC-III in HDL, which may cause increased production of inflammatory mediators and adhesion of monocytes to endothelial cells [54]. On the

contrary, taking statins (pitavastatin) not only increases HDL-C levels, but also enhances their antioxidant properties and ability to reverse cholesterol transport [55]. It should be noted that statins and niacin may exhibit prodiabetogenic effects [56]. Therefore, statin treatment increases the likelihood of developing diabetes when prescribed to people with risk factors for developing the disease [57]. It is proposed to determine the ability of HDL to carry out the outflow of cholesterol from cells as one of the key criteria for HDL functionality. Currently, methodological approaches aimed at identifying dysfunctional HDL are available only to research laboratories due to the complexity of execution and the lack of a universal standard methodology. Success in the search for biomarkers of HDL dysfunction is associated with the study of the proteomics and lipidome of these particles [14, 58]. Considering that HDL, in addition to participating in the transport of cholesterol, performs important regulatory functions in the body [59], there is reason to assume that the structural modification of HDL in diabetes is one of the reasons for the development of cardiovascular pathology and high mortality. Therapeutic approaches to prevent these complications may include the use of antioxidant drugs to prevent oxidative modification of HDL, as well as increasing HDL/apoA-I levels through gene therapy or administration of reconstituted HDL and recombinant apoA-I mimetics [60].

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