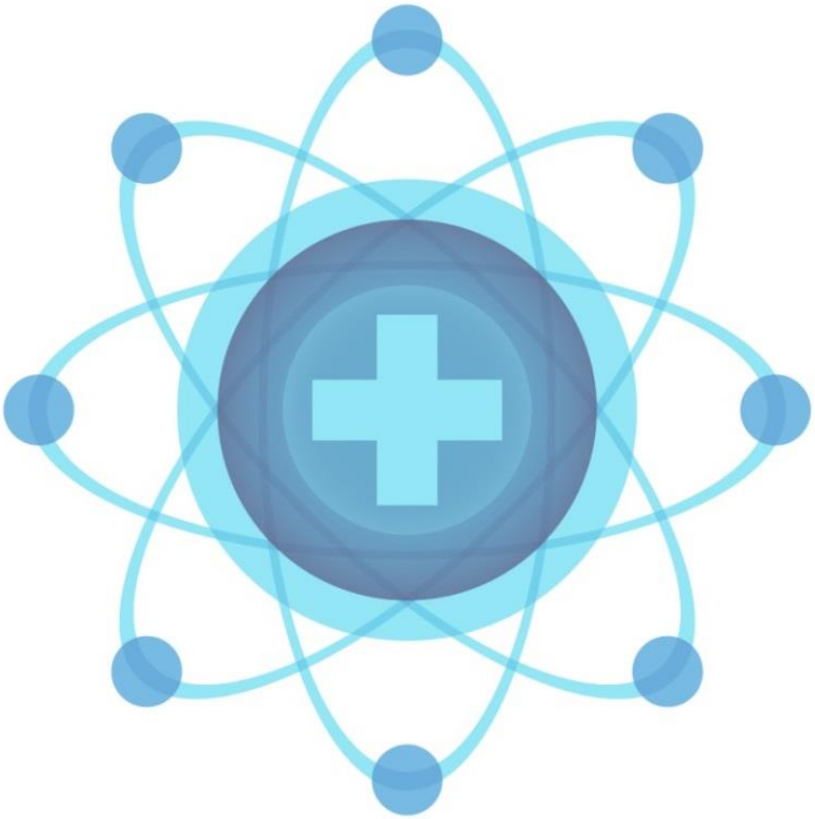

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# DYSLIPIDEMIA IN DIABETES MELLITUS TYPE 1

**F.A. Khaidarova, S.M. Khamraeva**

Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y.Kh. Turakulova

**Abstract:** Diabetes mellitus (DM) makes a significant contribution to global mortality statistics. According to the latest WHO data (2020) DM is the seventh most common cause of mortality. Atherogenic dyslipidemia is one of the main risk factors for cardiovascular disease in patients with type 1 and type 2 diabetes mellitus, in people with abdominal obesity, insulin resistance, or impaired glucose tolerance. In DM type 1 dyslipidemia has a quantitative and qualitative characteristic. This review article demonstrates the role of insulin in lipoprotein metabolism and quantitative lipid profile disorders in DM type 1 and their association with cardiovascular diseases.

**Keywords**: type 1 diabetes mellitus, dyslipidemia, markers, mechanism.

Diabetes mellitus is one of the most important problems on a global scale, which remains a serious disease that is dangerous for its outcomes, complications and leads to disability in the absence of timely diagnosis, proper treatment and lifestyle modification. Accordingly, DM makes a significant contribution to the mortality statistics of our population. According to the latest WHO data (2020), DM is the seventh most common cause of death [9] .

Cardiovascular disease (CVD) is a key cause of morbidity and mortality in both men and women with type 1 and type 2 diabetes. The risk of developing CVD in patients with type 2 diabetes is higher, while in patients with type 1 diabetes, intensive glycemic control contributes to a decrease in cardiovascular diseases. However, in patients with both type 1 and type 2 diabetes, other risk factors, including arterial hypertension and dyslipidemia, play an important role in the development of cardiovascular disease, and control of these risk factors is of paramount importance [11] .

Dyslipidemia is a cluster of lipid and lipoprotein abnormalities, including elevations in both fasting and postprandial triglycerides, apolipoproteins ( ApoB ), and low-density lipoproteins (LDL), as well as low levels of high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1) [7 ] . Atherogenic dyslipidemia is one of the major risk factors for cardiovascular disease in patients with type 2 diabetes mellitus and in people with abdominal obesity and insulin resistance or impaired glucose tolerance.

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Type 1 diabetes is an autoimmune disease resulting from the destruction of B cells in the pancreas. In type 1 diabetes, a high risk of developing cardiovascular diseases occurs, in particular, in patients with microalbuminuria and renal diseases [13] . According to a number of literary data, there is a close relationship between hyperglycemia and atherosclerosis.

Interestingly, women with type 1 DM have twice the risk of developing fatal and non-fatal vascular events compared with men with type 2 DM [27] . In addition, type 1 DM at a young age increases the risk of cardiovascular disease to a greater extent than type 1 DM that develops at a later age [12] . Approximately 20% of patients with type 1 diabetes are obese or overweight and 8% to 10% have criteria for the metabolic syndrome, including dyslipidemia, which increases the risk of developing cardiovascular disease in individuals with type 1 diabetes [15] .

According to studies of plasma lipid spectrum alteration, especially low levels of high-density lipoprotein (HDL) are associated with several inflammatory and immune diseases, including atherosclerosis and rheumatoid arthritis, suggesting a potential link between HDL and the body's immune system [ 3 ] . Moreover, it has become known that HDL has anti-inflammatory effects and will play an important role in protecting the body as part of the innate immune system. In addition, HDL inhibits the ability of antigen - presenting cells of the immune system to stimulate T cells. As a result, it was found that HDL and HDL-associated platelet activating factor acetyl hydrolase can restore the migration process of dendritic cells (DC) of the immune system and thus lead to the prevention of inflammatory processes in atherosclerotic plaques [6] .

While, studies have shown that the antioxidant and anti-inflammatory functions of HDL, in patients with type 1 and type 2 diabetes, are reduced [5] . Moreover, the ability of HDL to stimulate cholesterol efflux is reduced in patients with type 1 and type 2 diabetes [20] . Thus, these data indicate that HDL levels per se may not fully reflect the risk of cardiovascular disease in diabetic patients.

The lipid spectrum in patients with type 1 diabetes with good glycemic control is characterized by subnormal levels of triglycerides (TG) and LDL-C. While HDL-C is usually at the border of the upper norm or slightly elevated. This is explained by the fact that subcutaneous administration of insulin increases the activity of lipoprotein lipase in adipose tissue and skeletal muscle, and, consequently, the turnover rate of VLDL particles [8] .

**Role of insulin in lipoprotein metabolism**

Insulin plays an important role in the regulation of lipid metabolism. Insulin has anti-lipolytic, i.e. anabolic action by inhibiting the activity of hormone-sensitive lipase (HSL) in adipose tissue. Therefore, insulin reduces the secretion of free fatty acids from adipose tissue.

Moreover, postprandially in the gut, enterocytes produce large lipoproteins, chylomicrons , whose main apolipoprotein is apoB48. In circulation, lipoprotein lipase (LPL), which is produced by the liver, hydrolyzes triglycerides within the chylomicron , resulting in smaller particles. Remaining chylomicrons are taken up by the liver via LDL receptors or LDL receptor-related protein (LRP) [ 10].

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Thus, insulin significantly affects postprandial lipid metabolism, reducing chylomicron production by reducing LPL activity, which accelerates chylomicron catabolism by increasing the expression of the LDL receptor and LRP, which leads to increased catabolism of chylomicron residues .

Further, very low density lipoproteins (VLDL) are produced in the liver, the main apolipoprotein of which is apoB 100. In plasma, VLDL is hydrolyzed by LPL, which leads to the formation of intermediate density lipoproteins (IDL), which are further hydrolyzed through additional lipolysis, including hepatic lipase and converted into lipoproteins low density (LDL). Insulin inhibits the production of VLDL in the liver . The inhibition of VLDL production by insulin is due both to its anti-lipolytic action - which reduces circulating FFAs, which are substrates for VLDL - and to a direct inhibitory effect in liver cells through various mechanisms, including inhibition of the microsomal triglyceride transport protein [ 16 ] . In addition, insulin, which is a powerful LPL activator, promotes VLDL catabolism [ 24 ] .

Further, LDL is taken up by cells by binding to the LDL receptor on the plasma membrane of the liver. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a key role in regulating LDL receptor activity by binding to the LDL receptor and directing the receptor from recycling back to the surface and redirecting it to the lysosomal catabolic pathway.

Insulin increases the expression and activity of the LDL receptor and thus promotes LDL catabolism [25] .

HDL is synthesized by both the liver and the intestines, which contain only apo -lipoproteins (mainly apoA- I). HDL acquire cholesterol from peripheral tissues, including macrophages in arterial walls, via the ATP-binding cassette A1, membrane-bound (ABCA1) and G1 (ABCG1) transporters. Within the HDL particle, free cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT). HDL exchange lipids with VLDL in a process involving cholesterol ester transfer protein (CETP), whereby cholesterol esters are transferred from HDL to VLDL. Accordingly, triglycerides are transferred from VLDL to HDL. During this process, HDL is enriched in triglycerides, which are catabolized by hepatic lipase, thus forming small HDL particles that can be cleared by the liver via the scavenger B1 receptor (SR-B1).

In type 1 diabetes, dyslipidemia has a quantitative and qualitative characteristic. Several epidemiological studies have reported quantitative lipid abnormalities, i.e. imbalance between components of the lipid profile such as hypertriglyceridemia and elevated LDL cholesterol [ 21 ] . As shown in several studies, this imbalance of plasma lipids is mainly due to poor glycemic control [ 18 ] . Indeed, in a prospective study including 895 patients with type 1 DM, glycated hemoglobin ( HbA 1c ) was independently associated with LDL, decreased HDL, and triglycerides [ 18 ] . In a study of coronary artery calcification in type 1 diabetes, every 1% increase in HbA 1c was associated with an increase in LDL, a decrease in HDL, and an increase in triglycerides by 0.103 mmol/L, 0.129 mmol/L, and 0.052 mmol/L, respectively [ 14 ] . This indicates that hyperglycemia is an important factor leading to quantitative lipid abnormalities in type 1 DM. According to the literature,

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quantitative lipid disorders are observed in patients with type 1 diabetes, when the level of HbA 1 c is above 7.5%. In addition, some of the quantitative lipid abnormalities seen in some type 1 DM patients, such as hypertriglyceridemia , are likely associated with a subgroup of type 1 DM patients with metabolic syndrome.

Hypertriglyceridemia , which occurs in patients with type 1 diabetes with poor or suboptimal glycemic control, is primarily associated with an increase in VLDL production, which occurs secondary to relative insulin deficiency [24] . In addition, these patients have postprandial hyperlipidemia. Decreased clearance of postprandial lipoproteins (chylomicrons and VLDL) was observed in a radioisotope kinetic study conducted in type 1 DM patients with poor glycemic control [8] . In another study of type 1 DM patients with elevated HbA 1 c , a longer-term clearance of residual particles was reported, characterized by an increase in plasma apoB 48 at 6 h (+ 45%) and 8 h (+ 69%) after a sequential meal [17] . In adolescents with type 1 DM, triglycerides after a fatty meal were higher at HbA 1 c levels of more than 9.5%, compared with cases where, HbA 1c less than 8.7% [23].

There is evidence in the literature that glucose increases chylomicron production in healthy men [ 27 ] but does not modify chylomicron metabolism in patients with type 1 diabetes after a short-term deterioration in glycemic control [12]. Thus, dyslipidemia is detected in the presence of long-term poor glycemic control in type 1 DM.

In patients with type 1 diabetes with optimal glycemic control, plasma LDL is normal or slightly elevated [25]. This is a consequence of a decrease in the production of VLDL caused by peripheral hyperinsulinemia and an increase in LDL catabolism in patients with type 1 DM [7]. It is hypothesized that increased LDL catabolism may be due to an increase in LDL receptor expression as a consequence of peripheral hyperinsulinemia . This is supported by data showing a trend towards a decrease in LDL catabolism when switching from subcutaneous insulin injection to intravenous insulin infusion in patients with type 1 DM [6]. The level of plasma PCSK9 in patients with type 1 DM significantly correlates with the level of HbA1 c [11], which may become a marker for early detection of diabetic dyslipidemia in type 1 DM. The mechanism and reasons for the increase in PCSK9 levels are still unknown. In patients with good glycemic control, plasma levels of PCSK9 do not appear to be associated with LDL [ 10 ] but are negatively correlated with the proportion of dense small LDL particles [ 2 ] .

Plasma HDL-cholesterol levels are normal or elevated in well-controlled patients with type 1 diabetes [4] . Interestingly, some studies show that the increase in HDL-cholesterol levels in patients with type 1 DM is more pronounced in men than in women [26]. This increase in plasma HDL may be due to the increased ratio between LPL (lipoprotein lipase) and hepatic lipase, which is observed in patients with good glycemic control in type 1 diabetes [24] . Again, the increased LPL activity seen in patients is likely due to peripheral hyperinsulinemia that results from subcutaneous insulin administration.

Furthermore, in patients with type 1 DM, both plasma adiponectin and LPL activity have been shown to be positively associated with HDL levels [ 5 ] .

According to the literature, adiponectin is an independent factor associated with decreased HDL- apoA - I catabolism [ 1 ] , suggesting that adiponectin may play a role in elevated HDL levels in type 1 DM. However, as mentioned above, an elevated HDL level cannot be considered an " atheroprotective " marker in type 1 DM, since HDL particles found in patients with type 1 DM have significant damaged qualitative and functional disorders.

**Qualitative disorders of the lipid profile in type 1 diabetes.**

Patients with type 1 diabetes, even with good glycemic control, show qualitative lipoprotein abnormalities. These qualitative disturbances, not directed by optimal glycemic control, are potentially atherogenic.

In well-controlled type 1 DM, there are changes in the distribution of VLDL subfractions with a reduced concentration of large or medium-sized VLDL and an increased concentration of small-sized VLDL fractions [19]. This may be due to the fact that peripheral hyperinsulinemia reduces the level of free fatty acids in blood plasma and promotes LPL activity. Consequently, VLDL catabolism is enhanced. In addition, in patients with type 1 diabetes, we observe an increase in the ratio between free cholesterol and lecithin at the periphery of VLDL particles, which may reduce its fluidity and stability [22] .

**Conclusions.**

Thus, in patients with type 1 diabetes, lipid spectrum disorders play an important role in the risk of developing CVD. Quantitative lipoprotein abnormalities have been reported in type 1 DM patients with poor glycemic control. In type 1 diabetes with an optimal HbA 1c level, triglycerides and LDL cholesterol are within normal limits or slightly reduced, while HDL is normal or slightly elevated. Patients with type 1 diabetes have several qualitative and functional disorders of the lipid spectrum, which can potentially be atherogenic. Although the mechanisms underlying dyslipidemia in type 1 diabetes remain unclear, it is likely that the subcutaneous route of insulin administration, which is responsible for peripheral hyperinsulinemia , is an important factor in the development of this condition. Every year, interest in identifying new markers of diabetic dyslipidemia is growing. Thus, the level of plasma PCSK9 in patients with type 1 diabetes significantly correlates with the level of HbA1c, which can become a marker for early detection of diabetic dyslipidemia in type 1 diabetes.

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