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RISK FACTORS FOR LIPID METABOLISM DISORDERS OF DIFFERENT GENESIS OF ORIGIN (LITERATURE REVIEW)

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Abstract:

Lipid metabolism disorder is a condition characterised by disturbance of the ratio of atherogenic and non-atherogenic lipoproteins, which tends to develop in modern society. In modern medicine it is proved that dyslipidemias include a wide range of disorders, and they have a leading role in the development of cardiovascular and neurological diseases with severe complications. This factor alone or in combination with other factors creates the risk of atherosclerosis. In recent years, much attention has been paid to the detection and treatment of elevated total cholesterol (TC) and LDL-C. However, other forms of dyslipidaemia have also been shown to cause disease.

Keywords: hyperlipidaemia, hypolipidaemia, dyslipidaemia, pathogenesis, complications.

INTRODUCTION. Two types of lipid metabolism disorders are distinguished: primary and secondary hyperlipidaemia. Primary, or in other words, hereditary hyperlipidaemia, is based on the presence of genetic defects of one type or another that lead to deficiencies of enzymes, apolipoproteins and receptors. Familial hyperlipidaemia can be either monogenic or polygenic. Primary hyperlipidemia is characterised by pronounced disorders of lipid metabolism and the appearance of internal somatic signs (lipoid arc of the cornea, lipemia of retinal vessels, tuberous and tendon xanthomas of extensor surfaces of palm and knee joints, Achilles tendons, eruptive xanthomas all over the body, and xanthelasma of the eyelids).

MATERIALS AND METHODS: In the course of the study, the results obtained in domestic and foreign studies of recent years were studied. In order to analyse the aspects of pathogenesis of lipid metabolism disorders among published works, the results of systematic review and meta-analysis were mainly studied. The conclusions of this work were formed on the basis of data collection and systematisation. At the same time, the results of dissertation studies were also studied. Special attention was paid to the level of reliability of published works.

RESULTS OF THE STUDY. The most common forms of inherited disorders of lipid metabolism include familial hypercholesterolaemia (FH), familial combined hyperlipidaemia, familial hypertriglyceridaemia, hypoalphalipoproteinaemia and hyperlipidaemia III phenotype [17]. Some diseases, hormonal disorders, and medications may be accompanied by disorders of lipid metabolism. This type of disorders is classified as secondary hyperlipidaemia. Unlike primary disorders, secondary disorders of lipid metabolism are expressed at the level of mild to moderate severity, and somatic symptoms are not observed [2]. Diseases causing secondary disorders of lipid metabolism are divided into several groups: 1. Endocrine and metabolic diseases (hypothyroidism, pituitary hypofunction, DM, gout, obesity, alcoholism). 2. Kidney diseases (nephrotic syndrome, chronic kidney disease). 3. Acute illnesses (burns, infections). 4. Liver diseases (primary biliary cirrhosis, congenital bile duct atresia). 5. Other diseases (neurogenic anorexia, systemic lupus erythematosus).
In clinical practice, lipid metabolism disorders are diagnosed on the basis of lipid profile disorders, including triglycerides OX (TG), HDL-C and LDL-C. The latter is determined by the Friedwald formula.
Chronic kidney disease (CKD) is among the serious public health problems worldwide. Cardiovascular disease is known to be a major cause of morbidity and mortality in patients with CKD [4,17,20]. Thus, although a fraction of patients develop terminal renal failure, most of them die from cardiovascular disease. Dyslipidaemia is detected in 64% of cases in CKD patients, which is significantly higher compared to the general population. Hypertriglyceridaemia is one of the most frequent disorders of lipid metabolism in CKD patients [3,22,]. The concentration of triglyceride-rich lipoproteins (very low density lipoproteins (VLDL), chylomicrons and their remnants)) starts to increase in the early stages of CKD and reaches the highest values in patients with terminal renal failure. Several studies have shown that triglyceride levels are elevated in patients with renal dysfunction even if serum creatinine is within the reference values of normal [1,15]. In patients with CKD, total cholesterol levels are mostly

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normal or reduced, rarely elevated. A significant factor determining the amount of LDL-C in plasma is the degree of proteinuria. Chronic kidney disease has no significant effect on cholesterol metabolism in the absence of significant proteinuria. In addition, LDL-C receptor-dependent cholesterol uptake plays a key role in cholesterol homeostasis. CHBP does not alter LDL-CS receptor gene expression in the liver in the absence of significant proteinuria or marked glomerulosclerosis. In contrast, patients with nephrotic syndrome have an acquired deficiency of the LDL-CS receptor.

Diabetes mellitus (DM) is associated with a high risk of early development of atherosclerosis, especially coronary heart disease (CHD) and peripheral arterial disease. Dyslipidaemia in type II diabetes mellitus is characterised by high triglyceride levels and decreased HDL-C, with changes in the lipid profile observed long before the onset of clinically significant hyperglycaemia. The increase in triglycerides in patients with type II diabetes mellitus is due to the excretion of free fatty acids into the blood as a result of increased release of free fatty acids from adipose tissue and a decrease in their consumption by muscles. [19]. In response to this, the formation of LDL in the liver increases, leading to the development of marked hypertriglyceridaemia due to increased secretion of TG-rich lipoproteins into the bloodstream while lipolysis is suppressed. An increase in the concentration of atherogenic LDL-CS is also noted in type II DM. LDL-CS particles become finer and denser with increasing CH content, with a tendency to peroxidation. Glycosylated LDL is poorly recognised by apo B, E receptors in the liver and is more slowly eliminated from the bloodstream. They are more actively taken up by monocytes/macrophages, accumulate in the vessel wall and stimulate the process of atherosclerosis. Dyslipidaemia in type II DM is often accompanied by low concentrations of antiatherogenic LDL-C. Such changes in lipid metabolism are especially pronounced after meals, i.e. atherogenic postprandial hyperlipidaemia develops [18].

Thyroid hormones are known to be inducers of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase, thus participating in the first stage of cholesterol synthesis. In addition, triiodothyronine (T3), being a regulator of LDL receptor activity, controls the activity of the genes responsible for them and protects LDL from oxidation. Another important aspect is that thyroid hormones stimulate the conversion of cholesterol into bile acids. It has been found that T3 regulates the activity of cholesterol-7 α-hydroxylase, the most important enzyme of bile acid synthesis, so that in hypothyroidism cholesterol metabolism in the liver slows down, resulting in an increase in its amount in the blood [12,33].

Salter A. et al. report that thyroid hormones increase LDL uptake by hepatocytes. Hypothyroidism is characterised by a decrease in LDL receptor density in hepatocytes, and compared to euthyroidism in the subclinical form, a higher concentration of lipoprotein-associated A2 (Lp-PLA2) phospholipase is detected, which is known as a marker of CHD in the subclinical stage of hypothyroidism [22].

Thus, thyroid hormone deficiency contributes to the development of hypercholesterolaemia, and this is one of the characteristic manifestations of hypothyroidism; in this case, the higher the level of TTH, the higher the cholesterol level [7]. In addition, T3 activates apolipoprotein A, which plays a key role in controlling triglyceride levels.

The association between subclinical hypothyroidism and dyslipidaemia has been proven in numerous studies and is evident when thyroid hormone (TSH) levels are above 10 IU/L. Almost all hypothyroid patients, including those with subclinical hypothyroidism, have lipid metabolism disorders: low levels of total cholesterol, HDL-C, triglycerides and LDL-C [18]. The results of the Norwegian population-based HUNT study show that the relationship between TSH levels and blood lipid levels in individuals without thyroid disease and CVD was also determined at normal TSH values: the higher the TSH level, the higher the cholesterol level. Dyslipidaemia in hypothyroidism is considered atherogenic. The same HUNT study found a direct association between TTG levels within reference values and the risk of mortality from CHD in women with undiagnosed thyroid disease. Several large studies have shown that dyslipidaemia in hypothyroidism increases the risk of atherosclerosis, CHD and myocardial infarction (MI). A meta-analysis of studies conducted between 1950 and May 2010, including 287 patients aged 55 years with subclinical hypothyroidism from the USA, Europe, Australia, Brazil, and Japan, showed an increased relative risk of CHD and CVD mortality independent of sex, age, and CVD [32].

Obese patients (body mass index (BMI) 30 kg/m2 and higher) often develop atherogenic dyslipidaemia [8,26]. Against the background of increasing body weight, the concentration of TG in the blood increases and the level of HDL-CS decreases. In parallel with the increase in body weight, the release of free fatty acids (FFAs) from adipocytes into the bloodstream increases, which is accompanied by increased synthesis of LDL-C in the liver. This process is supported by low activity of peripheral lipoprotein lipase, which is unable to completely break down TG-rich particles. The amount of OX is often within the normal range, the increase in body weight for every 10% is accompanied by an increase in total plasma cholesterol by 0.3 mmol/L. Especially pronounced proatherogenic disorders in the system of lipid metabolism in the form of hypertriglyceridaemia and increased apo-B

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concentration are found in abdominal type of obesity [11, 28].

Long-term use of some drugs, including those for the treatment of CVDs, can also be the cause of secondary hyperlipidaemia. These include some antihypertensive agents (thiazides [27], anabolic steroids, non-selective beta-adrenoblockers-propranolol [5,13]), immunosuppressants (cyclosporine [14], prednisolone [9]), hormone replacement therapy containing estrogen and progesterone. Antipsychotic and anticonvulsant drugs also have the same effect. Changes in lipid levels on the background of taking drugs are considered mild: an increase in triglycerides by 15-30% and cholesterol by 6-10%. As a rule, withdrawal of these drugs leads to normalisation of the lipid spectrum [34]. Dietary patterns are also a factor in determining the amount of lipids in the blood. Clarke R. Et, al., a meta-analysis of 395 studies on the effect of diet composition on blood lipid levels, showed that an increase in saturated fat was associated with a significant increase in LDL-C, while an increase in unsaturated fat in the diet significantly reduced LDL-C and increased HDL-C levels. In a study by Sacks F.M. and Katap M., comparing different dietary options offered to patients in various randomised clinical trials, the Mediterranean diet and low-fat diet were characterised by a reduction in LDL-C by 11% and 9%, respectively, compared to the control group. [34].

Excessive alcohol consumption may also be one of the causes of dyslipidaemia; This type of dyslipidaemia is primarily characterised by hypertriglyceridaemia. In addition, chronic alcohol consumption can lead to obesity, fatty liver dystrophy, which in turn affects lipid metabolism as well [11]. Most smokers have hyperlipidaemia. In smokers peroxidation processes of LDL-CS are increased. Peroxide modified LDL have a high atherogenic potential, have a cytotoxic effect on the arterial wall and contribute to the development of atherosclerosis. Also in smokers, LDL-C levels are significantly decreased and triglyceride levels are increased. Compared to other factors affecting lipid levels such as alcohol consumption, BMI and age, smoking had the greatest influence and was an independent risk factor for dyslipidaemia [13].

Unlike secondary hyperlipidaemia caused by external factors and comorbidities, familial hypercholesterolaemia is a genetic autosomal dominant disease due to mutation of genes affecting LDL metabolism and LDL receptor activity [29].

"GHS is rarely diagnosed in Russia, there is no unified system of registration of such patients, therefore the true prevalence of the disease remains unknown. With a Russian population of 143.5 million people (according to Rosstat, 2013), the number of patients with heterozygous CHC (with a fixed incidence of 1:500) is 287,000, and patients with homozygous CHC can reach ~ 143-287 (1:500 thousand) -1 million). According to Boytsov S.A. et al., out of 2400 people who applied to the polyclinic for all health-related issues, the level of OH >7.5 mmol/l was diagnosed in 12% and in 10% of persons with LDL-C >4.9 mmol/l. Currently, two approaches are used to identify patients with HCS: the use of phenotype, that is, traits determined by the severity of exposure and duration of exposure to hypercholesterolaemia, or genotype, that is, the body's response to the presence of high cholesterol levels and the risk of ischaemic complications. To date, the most commonly used criteria for the diagnosis of HCC are the British criteria (Simon Broome Registry) [31] and the Dutch Lipid Clinic Network (DLCN) criteria [30]. According to the recommendations of the International Foundation's General Recommendations for the Treatment of Familial Hypercholesterolaemia, both phenotypic criteria and genetic tests can be used for the most accurate diagnosis of HCV; if genetic tests are not available, the diagnosis can be confirmed phenotypically, and secondary hypercholesterolaemia should be excluded first of all (recommendation class-I, level of evidence -A) [35].

CONCLUSIONS. Thus, the results of the studies indicate the necessity of screening for GHS in order to actively identify possible causes of secondary dyslipidemia, as well as the subsequent correction of the identified etiological factors, which significantly increases the effectiveness of hypolipidemic treatment and reduces the incidence of cardiovascular disease, complications in the distant period, as well as allows to start hypolipidemic therapy as early as possible in patients with familial forms of hypercholesterolemia.

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