

Risk Factors and Main Aspects of Lipid Metabolism Disturbances (Literary Review)

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Article History	Abstract
<p>Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 25 Nov 2023</p> <p>CC License CC-BY-NC-SA 4.0</p>	<p><i>Dyslipidemia is a disease characterized by a violation of the ratio of atherogenic and non-atherogenic lipoproteins, which tends to develop in modern society. In modern medicine, it has been proven that dyslipidemias include a wide range of disorders, and they play 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 cholesterol. However, it has been proven that other forms of dyslipidemia can also cause the development of diseases.</i></p> <p>Keywords: Hyperlipidemia, Hypolipidemia, Dyslipidemia, Pathogenesis, Complications</p>

1. Introduction

There are two types of lipid metabolism disorders: primary and secondary hyperlipidemia. Primary, or in other words, hereditary hyperlipidemia, is based on the presence of genetic defects of one type or another, which lead to a deficiency of enzymes, apolipoproteins and receptors. Familial hyperlipidemia can be either monogenic or polygenic. Primary hyperlipidemia is characterized by pronounced disorders of lipid metabolism and the appearance of internal somatic signs (lipoid arch of the cornea, lipemia of retinal vessels, tuberous and tendon xanthomas of the extensor surfaces of the palmar and knee joints, Achilles tendons, eruptive xanthomas throughout the body, and xanthelasmas of the eyelids).

2. 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 analyze aspects of the pathogenesis of lipid metabolism disorders among the published works, the results of a systematic review and meta-analysis were mainly studied. The conclusions of this work were formed on the basis of data collection and systematization. At the same time, the results of dissertation research were also studied. Particular attention was paid to the level of reliability of published works.

3. Results and Discussion

The most common forms of hereditary lipid disorders include familial hypercholesterolemia (FH), familial combined hyperlipidemia, familial hypertriglyceridemia, hypoalphalipoproteinemia, and phenotype III hyperlipidemia [17]. Some diseases, hormonal disorders, taking medications may be accompanied by lipid metabolism disorders. This type of disorder is classified as secondary hyperlipidemia. Unlike primary, secondary disorders of lipid metabolism are expressed at the level of mild and moderate severity, and no somatic symptoms are observed [2]. Diseases that cause secondary disorders of lipid metabolism are divided into several groups: 1. Endocrine and metabolic diseases (hypothyroidism, pituitary hypofunction, diabetes, gout, obesity, alcoholism). 2. Diseases of the kidneys (nephrotic syndrome, chronic kidney disease). 3. Acute diseases (burns, infections). 4. Diseases of the liver (primary biliary cirrhosis of the liver, congenital atresia of the bile ducts). 5. Other diseases (anorexia nervosa, systemic lupus erythematosus).

In clinical practice, lipid metabolism disorders are diagnosed on the basis of lipid profile disorders, including triglycerides (TG), HDL-C and LDL-C. The latter is determined by the Friedwald formula. Chronic kidney disease (CKD) is one of the major public health problems worldwide. It is known that cardiovascular diseases are one of the main causes of morbidity and mortality in patients with CKD [4,17,20]. Thus, although some patients develop end-stage renal failure, most of them die from cardiovascular diseases. Dyslipidemia is detected in 64% of cases in patients with CKD, which is significantly higher compared to the general population. Hypertriglyceridemia is one of the most common disorders of lipid metabolism in patients with CKD [3,22,]. The concentration of triglyceride-rich lipoproteins (very low density lipoproteins (VLDL), chylomicrons and their residues)) begins to increase in the early stages of CKD and reaches its highest values in patients with end-stage renal disease. Several studies have shown that in patients with impaired renal function, even if serum creatinine is within the reference range, triglyceride levels are elevated [1,15]. In patients with CKD, the level of total cholesterol is mostly normal or low, in rare cases it is elevated. An important factor determining the amount of LDL-C in plasma is the degree of proteinuria. Chronic kidney disease does not significantly affect cholesterol metabolism in the absence of severe proteinuria. In addition, LDL-C receptor-dependent cholesterol uptake plays a key role in cholesterol homeostasis. CKD does not alter LDL-C receptor expression in the liver in the absence of severe proteinuria or severe glomerulosclerosis. On the contrary, in patients with nephrotic syndrome, an acquired deficiency of the LDL-C receptor is observed. Diabetes mellitus (DM) is associated with a high risk of early development of atherosclerosis, especially coronary heart disease (CHD) and peripheral arterial disease. Dyslipidemia in type II diabetes mellitus is characterized by high triglyceride levels and a decrease in HDL-C, with changes in the lipid profile observed long before the onset of clinically significant hyperglycemia. An increase in the amount of triglycerides in patients with type II diabetes mellitus is due to the excretion of free fatty acids into the blood as a result of an increase in the release of free fatty acids from adipose tissue and a decrease in their consumption by muscles. [19]. In response to this, the formation of VLDL in the liver increases, which leads to the development of severe hypertriglyceridemia due to increased secretion of TG-rich lipoproteins into the bloodstream while suppressing lipolysis. An increase in the concentration of atherogenic LDL cholesterol is also noted in type II diabetes.

The LDL-XC particles become smaller and denser as the XC content increases, with a tendency to peroxide. Glycosylated LDL is poorly recognized by apo B, E receptors in the liver and is more slowly removed from the bloodstream. They are more actively captured by monocytes/macrophages, accumulate in the vessel wall and stimulate the process of atherosclerosis. Dyslipidemia in type II DM is often accompanied by low concentrations of the anti-atherogenic LDL-C. Such changes in lipid metabolism are especially pronounced after a meal, that is, atherogenic postprandial hyperlipidemia develops [18]. E receptors in the liver and is more slowly removed from the bloodstream. They are more actively captured by monocytes/macrophages, accumulate in the vessel wall and stimulate the process of atherosclerosis. Dyslipidemia in type II DM is often accompanied by low concentrations of the anti-atherogenic LDL-C. Such changes in lipid metabolism are especially pronounced after a meal, that is, atherogenic postprandial hyperlipidemia develops [18]. It is known that thyroid hormones are inducers of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase, thereby participating in the first stage of cholesterol synthesis. In addition, triiodothyronine (T3), being a regulator of the activity of LDL receptors, 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 established that T3 regulates the activity of cholesterol-7 α - hydroxylase, the most important enzyme in the synthesis of bile acids, as a result of which, in hypothyroidism, the metabolism of cholesterol in the liver slows down, as a result of which its amount in the blood increases [12,33]. Salter A. et al. reported that thyroid hormones increase LDL uptake by hepatocytes. Hypothyroidism is characterized by a decrease in the density of LDL receptors in hepatocytes, and, compared with euthyroidism in subclinical form, a higher concentration of lipoprotein-associated A2 (Lp-PLA2) phospholipase, which is known as a marker of coronary artery disease in the subclinical stage of hypothyroidism, is detected [22].

So, the lack of thyroid hormones contributes to the development of hypercholesterolemia, and this is one of the characteristic manifestations of hypothyroidism; at the same time, the higher the TSH level, the higher the cholesterol level [7]. In addition, T3 activates apolipoprotein A, which plays a key role in triglyceride control. The relationship between subclinical hypothyroidism and dyslipidemia has been proven in numerous studies and appears when the level of thyroid-stimulating hormone (TSH) is above 10 IU/l. Almost all patients with hypothyroidism, including those with subclinical hypothyroidism, have lipid metabolism disorders: low levels of total cholesterol, SWL-C, triglycerides, and LDL-C [18]. The results of the HUNT population study conducted in Norway show that the relationship between TSH levels and blood lipid levels in individuals without thyroid disease and CVD was also determined with normal TSH values: the higher the TSH level, the higher the cholesterol level. Dyslipidemia in hypothyroidism is considered atherogenic. In the same HUNT study, a direct relationship was found between TSH levels within reference ranges and the risk of death from coronary artery disease in women with undiagnosed thyroid disease. Several large studies have shown that dyslipidemia in hypothyroidism increases the risk of atherosclerosis, coronary artery disease, 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 death from coronary artery disease and CVD, regardless of gender, age and CVD [32]. Patients with obesity (body mass index (BMI) 30 kg/m² and above) often develop atherogenic dyslipidemia [8,26]. Against the background of an increase in body weight, the concentration of TG in the blood increases and the level of HDL cholesterol decreases. In parallel with an increase in body weight, the release of free fatty acids (FFA) from adipocytes into the bloodstream increases, which is accompanied by increased synthesis of VLDL in the liver. This process is supported by the low activity of peripheral lipoprotein lipase, which is not able to completely cleave TG-rich particles. The amount of OH is often within the normal range, an increase in body weight for every 10% is accompanied by an increase in total cholesterol in the blood plasma by 0.3 mmol / l.

Long-term use of certain drugs, including those for the treatment of CVD, can also be the cause of secondary hyperlipidemia. These include some antihypertensive agents (thiazides [27], anabolic steroids, non-selective beta-blockers-propranolol [5,13]), immunosuppressants (cyclosporine [14], prednisolone [9]), hormone replacement therapy containing estrogen and progesterone. Also, antipsychotic and anticonvulsant drugs have the same effect. Changes in lipid levels while taking drugs are considered mild: an increase in triglycerides by 15-30% and cholesterol by 6-10%. As a rule, the abolition of these drugs leads to the normalization of the lipid spectrum [34]. Nutritional characteristics are also one of the factors that determine the amount of lipids in the blood. Clarke R. Et, al., a meta-analysis of 395 studies looking at the effect of dietary composition on blood lipid levels found that an increase in saturated fat was associated with a significant increase in LDL-C, while an increase in dietary unsaturated fat significantly reduced LDL-C and increased HDL-C. In a study by Sacks FM and Catan M. comparing different dietary options offered to patients in various randomized clinical trials, the Mediterranean diet and the low-fat diet were characterized by a reduction in LDL cholesterol by 11% and 9%, respectively, compared with the control group. [34]. Excessive alcohol consumption can also be one of the causes of dyslipidemia; This type of dyslipidemia is primarily characterized by hypertriglyceridemia. In addition, chronic alcohol consumption can lead to obesity, fatty degeneration of the liver, which in turn affects lipid metabolism [11]. Most smokers have hyperlipidemia. In smokers, the processes of peroxidation of LDL cholesterol are enhanced. Peroxide modified LDL have a high atherogenic potential, have a cytotoxic effect on the arterial wall and contribute to the development of atherosclerosis. Smokers also have significantly reduced LDL cholesterol levels and increased triglyceride levels. Compared to other factors influencing lipid levels, such as alcohol consumption, BMI, and age, smoking had the largest impact and was an independent risk factor for dyslipidemia [13].

Unlike secondary hyperlipidemia caused by external factors and concomitant diseases, familial hypercholesterolemia is a genetic autosomal dominant disease caused by mutations in genes that affect LDL metabolism and the activity of their receptors [29]. HCS is rarely diagnosed in Russia, there is no unified registration system for such patients, and therefore the true prevalence of the disease remains unknown. With a population of Russia of 143.5 million people (according to Rosstat, 2013), the number of patients with heterozygous CHC (with a fixed frequency 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 TC > 7.5 mmol/l was diagnosed in 12% and in 10% of individuals with LDL-C > 4.9 mmol/l. Currently, two approaches are used to identify patients with HCH: using the phenotype, that is, signs

determined by the severity of exposure and duration of exposure to hypercholesterolemia, or genotype, that is, the body's response to the presence of high cholesterol and the risk of ischemic complications. To date, the following criteria are most commonly used for the diagnosis of HCH: the British criteria (Simon Broome Registry) [31] and the Dutch criteria Dutch Lipid Clinic Network (DLCN) [30]. According to the recommendations of the "General recommendations for the treatment of familial hypercholesterolemia" of the International Foundation, for the most accurate diagnosis of HCH, both phenotypic criteria and genetic tests can be used, if it is not possible to conduct genetic studies, the diagnosis can be confirmed phenotypically, and first of all, secondary hypercholesterolemia (recommendation class-I, level of evidence-A) [35]. To date, the following criteria are most commonly used for the diagnosis of HCH: the British criteria (Simon Broome Registry) [31] and the Dutch criteria Dutch Lipid Clinic Network (DLCN) [30]. According to the recommendations of the "General recommendations for the treatment of familial hypercholesterolemia" of the International Foundation, for the most accurate diagnosis of HCH, both phenotypic criteria and genetic tests can be used, if it is not possible to conduct genetic studies, the diagnosis can be confirmed phenotypically, and first of all, secondary hypercholesterolemia (recommendation class-I, level of evidence-A) [35].

4. Conclusion

Thus, the results of the studies indicate the need for screening for HCH 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 lipid-lowering treatment and reduces the incidence of cardiovascular diseases, complications in the long-term period, as well as allows you to start lipid-lowering therapy as early as possible in patients with familial forms of hypercholesterolemia.

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