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Secondary hyperlipidemia: definition, phenotypes, and inducing factors

Mal G. S., Smakhtina A. M.

Kursk State Medical University of the Ministry of Healthcare of Russia Federation, Kursk, Russia.

Authors

Galina S. Mal*, doctor of medical science, professor, Head of the Department of Pharmacology of the Kursk State Medical University of the Ministry of Healthcare of Russia Federation, Kursk, Russia.

Angelina M. Smakhtina, laboratory assistant of the Scientific and Research Institute of Experimental Medicine, Kursk State Medical University of the Ministry of Healthcare of Russia Federation, Kursk, Russia.

Abstract. *The investigations related to lipid metabolism disorders have been relevant for many years, due to its correlation with cardiovascular risk and the leading positions of cardiovascular mortality. Timely diagnosis and treatment of dyslipidemia increases therapy effectiveness and, therefore, improves the quality and increases life expectancy. This review article examines current understanding of the secondary dyslipidemia phenotypes and its causes.*

Key words: *secondary hyperlipidemia, risk factors for dyslipidemia, phenotypes of secondary hyperlipidemia.*

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Cardiovascular diseases (CVDs) are still the leading cause of death and disability. According to Rosstat, 938538 people deceased due to CVDs in 2020 that by 11.6% higher than in 2019 [11, 33]. The increase of cardiovascular mortality may be associated with the COVID-19 pandemic, since this disease is accompanied by multiorgan failure, including the cardiovascular system (CVS) [4]. High prevalence of CVDs ensues the need for preventive measures aimed to improve the quality of patient's life by minimizing modifiable risk factors.

At this stage, dyslipidemia (DLP) is considered as the main factor in the development and progression of atherosclerosis in patients with various diseases, therefore, the improvement of lipid profile is essential for the reduction of cardiovascular risk [7]. In recent years, the prevalence of diabetes mellitus (DM), obesity, etc. has significantly increased that contributed to the rise of the diseases predisposing to the development of secondary hyperlipidemias (HLP) [10]. The epidemiological ESSE-RF study established high prevalence of atherogenic dyslipidemias in

* Corresponding author. Tel. +7(960) 676-1698. E-mail: mgalina.2013@mail.ru

Table 1. **The Frendrickson classification of hyperlipidemias recommended by WHO and the most common causes of lipid metabolism disorders development and progression**

Type	Synonym	Elevated plasma lipoprotein	Plasmatic cholesterol and triglycerides	Atherogenicity	DLP structure (%)	Secondary causes
I	Hyperchylomicronemia	Chylomicrones	TG, TC	—+	<1	Systemic lupus erythematosus
IIa	Hypercholesterolemia	LDL	TC	+++	10	Hypothyroidism
IIb	Combined hyperlipidemia	LDL, VLDL	TC, TG	+++	40	DM, nephrotic syndrome, anorexia nervosa
III	Familial dysbetalipoproteimemia	IDL	TG, TC	+++	<1	Abdominal obesity, DM, hypothyroidism
IV	Familial hypertriglyceridemia	VLDL	TG	+	45	CKD, DM, alcohol
V	Combined hyperlipidemia	Chylomicrones, VLDL	TG, TC	+	5	Thiazide diuretics, oral contraceptives, beta-blockers, alcohol

HDL-high density lipoproteins, LDL — low density lipoproteins, TG — triglycerides, TC — total cholesterol, VLDL — very low-density lipoproteins, IDL — intermediate-density lipoproteins, DM — diabetes mellitus, CKD — chronic kidney disease.

Table 2. **Modern classification of hyperlipidemias**

Type	TC	LDL	TG	HDL
Hypercholesteremia	+	+	Within reference values	Within reference values
Hypertriglyceridemia	Within reference values	Within reference values	+	Within reference values
Combined hyperlipidemia	+	+	+	Within reference values
Atherogenic hyperlipidemia	+ / Within reference values	+ / Within reference values	+	Decreased

HDL-high density lipoproteins, LDL — low density lipoproteins, TG — triglycerides, TC — total cholesterol

Russian Federation [26]. According to various sources, up to 30% of people with DLP have secondary hyperlipidemia [5]. The study of DLP becomes even more relevant during the COVID-19 pandemic, since DLP decrease organism's environmental resistance and increases the risk of viral infection [2, 38].

This review article presents current understanding of the secondary dyslipidemia phenotypes and its causes.

The definition of secondary hyperlipidemia

Secondary hyperlipidemia is the disorder of lipid metabolism induced by certain diseases, hormonal changes, and medication. It is necessary to differ primary (hereditary) and secondary (acquired) hyperlipidemia, since its management varies depending on the etiology [21]. Changes of lipid metabolism are usually of moderate severity and atherosclerotic plaques may not be present in patients with secondary hyperlipidemia unlike those with primary hyperlipidemia. However, as the pathological process develops, atherogenesis starts.

Secondary hyperlipidemia phenotypes

There are several classifications of hyperlipidemia. Currently, the World Health Organization (WHO) has approved the classification developed by D. Frendrickson (1965) that is based on the biochemical signs of DLM [21]. However, this classification is rarely used in everyday clinical practice, since there are several difficulties associated with the technique [5]. Therefore, Frendrickson's classification is more often used for scientific research. It should be noted that the classification (Table 1) establishes the type of hyperlipidemia regardless of etiology, as well as the risk of atherogenesis depending on the type of DLM: IIa, IIb and III types are atherogenic; I, IV and V types are "relatively" atherogenic [21].

Today, simplified version based on fasting lipid pannel (total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL)) is used. This classification includes predominant hypercholesteremia, predominant hypertriglyceridemia, combined hyperlipidemia and atherogenic hyperlipidemia (Table 2) [7] It is based on clinical studies indicating different degree of cardiovascular risk depending on the increase of various lipid fractions [5].

Inducing factors

The most common endocrine causes of hyperlipidemia include: hypothyroidism, Cushing's syndrome, uncontrolled diabetes mellitus (DM), obesity, hyperparathyroidism, growth hormone deficiency, pregnancy [5]. Certain medications can also induce the development of secondary hyperlipidemia such as: non-selective beta-blockers without intrinsic sympathomimetic activity, glucocorticoids, estrogens, psy-

chotropic medications, anabolic steroids, antiretroviral medications (protease inhibitors), thiazide diuretics, cyclosporine, barbiturates, cimetidine, retinoids [7 23, 24]. Other conditions that induce the development of hyperlipidemia are: chronic kidney disease, primary biliary cholangitis, biliary atresia, systemic lupus erythematosus, anorexia nervosa, arterial hypertension, paraproteinemia, burns, infections, alcohol abuse, smoking, carbohydrates and trans fats rich diet [1, 10, 20, 29]. We believe that it is important to assess the contribution of various risk factors to the development of pathological conditions associated with lipid metabolism disorders, based the latest literature data.

Diet impairment

Diet, alcohol consumption, and chronic stress contribute significantly to the development of DLM.

Trans fats

Trans fats induce the synthesis of endogenous cholesterol by the liver and apolipoprotein B (ApoB-100) that increases LDL cholesterol and atherogenic index and decreases HDL cholesterol.

Saturated fats

Saturated fatty acids affect the translation of LDL cholesterol receptors by decreasing the expression of mRNA that causes the elevation of their concentration. It should be emphasized that, not only molecular changes, but also the metabolism of saturated fatty acids contributes to the development of hyperlipidemia: chylomicrons and VLDL (very low-density lipoproteins) cholesterol, which have small size and high atherogenicity, are formed during the processing of saturated fats [7].

Fast digesting carbohydrates

The consumption of high glycemic index foods increases the secretion of insulin by the pancreas and activates GLUT-4 transporter that supplies glucose into adipose and muscle tissue cells. Due to the increased synthesis of reduced nicotinamide adenine dinucleotide (NADH), the monosaccharides convert into fatty acids and cause hypertriglyceridemia [9].

Alcohol

Alcohol abuse negatively affects blood triglyceride levels, causing hypertriglyceridemia. Ethanol damages hepatocyte mitochondria, impairs the oxidation of fatty acids and leads to hepatic steatosis [7]. The reduced NADH is produced by the metabolism of ethanol that triggers the biosynthesis of fatty acids. Acetaldehyde, a metabolite formed during ethanol catabolism, activates lipogenesis by suppressing the genes involved in fatty acid metabolism. Due to active synthesis of fatty acids, malonylcoenzyme A accumulates and suppresses their transport into mitochondria, which leads to their increase in blood plasma [6, 32]. Alcohol reduces the secretion of VLDL cholesterol by inhibiting the synthesis of apolipoproteins and phosphatidylcholine, the main phospholipid of cell membranes [10, 32].

Stress

Stress promotes the development of DLM through the increase of glucocorticoids, catecholamines and neuropeptide Y that enhance appetite and lead to stress-related overeating, primarily with high in saturated fat and cholesterol foods. It should be noted that stress hormones affect the hypothalamic-pituitary-adrenal axis, causing the increase of triglycerides blood concentration [10].

Internal diseases that cause of secondary dyslipidemias

The main diseases that affect lipid metabolism are presented in table 3 [10, 12, 14, 18, 19, 27, 28, 36, 37], however, certain disorders should be described further in detail.

COVID-19

Articles dedicated to the investigation of the new coronavirus infection (caused by SARS-CoV-2 virus) are of special relevance nowadays since the pandemic plays an important social, medical and economic role [16]. Foreign studies analyzed lipid profile in patients with a confirmed diagnosis of COVID-19. The following data were obtained in such patients: hypertriglyceridemia, decreased level of TC and HDL cholesterol, and elevated VLDL cholesterol. It is with noting the approximately 2 time increase of the Apo-B to Apo-A1 ratio that indicates the elevation of cardiovascular risk in patients with COVID-19 [3, 34]. Such changes may be partially explained by hepatopathy that is often observed in patients with SARS-CoV-2 [22].

Acquired immunodeficiency syndrome (AIDS)

It is well-known fact that antiretroviral pharmacotherapy can induce the development of secondary hyperlipidemia [15]. But there is also evidence that human immunodeficiency virus (HIV) can cause dys-

lipidemia itself. Patients have elevated level of triglycerides and reduced level of HDL and LDL cholesterol. There is an opinion that the pathogenesis of lipid metabolism disorders in patients with HIV infection is associated with increased production of interferon α that limits triglyceride clearance [13].

Obesity

Triglycerides accumulate in the liver due to increased concentration of free fatty acids in the blood in patients with obesity. This stimulates the secretion of VLDL cholesterol that inhibits the lipolysis of chylomicrons due to competitive inhibition of LPL. Lipolysis is complicated by decreased expression of lipoprotein lipase mRNA in adipose and muscle tissue. The level of HDL and LDL cholesterol as well as TG decrease due to the exchange of esters by CETP between high, low and very low-density lipoproteins. DLM in patients with obesity is typical for metabolic syndrome (MS) [10].

Type 2 diabetes mellitus

Endocrine disorders occupy a special place among the causes of lipid metabolism disorders due to high prevalence, especially type 1 and type 2 diabetes mellitus. Dyslipidemia develops in 72–85 % of patients with type 2 diabetes mellitus [10]. The insulin effect decreases and induces lipolysis and the synthesis of VLDL cholesterol, their catabolism decreases due to low LPL activity and the elevation of ApoC–III level, therefore, the atherogenic index increases. The activity of intestinotrophic hormone, glucagon-like peptide 2 (GLP-2), increases with insulin resistance, and the concentration of ApoB48 rises. Increased secretion of ApoB48 and the expression of the microsomal triglyceride transfer protein stimulates the synthesis of chylomicrones that contributes to the development of postprandial hyperlipidemia [25]. Due to low lipoprotein lipase activity and elevated plasma levels of ApoC–III, an LPL inhibitor, chylomicron catabolism decreases in patients with insulin resistance [10].

The CETP activity in patients with hypertriglyceridemia together with hepatic lipase activity results in the formation of small dense LDL cholesterol and the reduction of large cholesterol-rich HDL cholesterol [18]. Patients with type 2 diabetes have HDL cholesterol with impaired ability to acquire cholesterol from cells that can be explained by decreased expression of the membrane ABCA1 transporter, which is responsible for the first stage of cholesterol transfer from cell membranes to HDL cholesterol. The decrease of the ABCA1 activity may be associated with its glycation.

Type 1 diabetes mellitus

The lipid profile of patients with type 1 diabetes is usually within reference values [10] due to the effects of subcutaneous insulin infusions (Table 3). However, in severe cases, insufficient insulin levels or the development of insulin resistance can lead to atherogenic hyperlipidemia [12].

Hypothyroidism

Uncompensated hypothyroidism is associated with low life quality and significant cardiometabolic disorders. The degree of dyslipidemia is affected by the severity of hypothyroidism, age, lifestyle (physical activity and nutrition) and genetic background [24]. Reduced expression of CYP7A1, which encodes the key enzyme of bile acid anabolism, and genes that code ATP-binding cassette transporters (ABCG5 / 8), which transfer cholesterol from hepatocytes to bile, increases the level of plasma cholesterol. Low serum thyroid hormone levels lead to lipoprotein lipase inactivation due to the expression genes that inhibit it [10].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) can be considered as hepatic type of metabolic syndrome that manifests with intrahepatic lipid accumulation (steatosis, fatty liver degeneration) in patients without other liver diseases and alcohol abuse. Atherogenic hyperlipidemia usually develops (see Table 3). It should be emphasized that the concentration of adiponectin with antiatherogenic properties [27, 31] is reduced compared with healthy controls, despite intense lipolysis and high fatty acid concentrations associated with increased fatty acid oxidation. Thus, low levels of adiponectin in patients with NAFLD can be considered as factors that limit the ability to increase lipid oxidation in response to fatty acid overload, and that induce their transesterification.

Cholestasis

Hyperlipidemia in patients with cholestasis is associated with the inhibition of 7-alpha-hydroxylase by bile acids that accumulate in the liver. The hydroxylase catalyzes the rate-limiting step in bile acid biosynthesis from cholesterol. Bile acids affect hepatic nuclear farnesoid X receptors (FXR) and inhibit the expression of the CYP7A1 gene encoding this enzyme [17]. Fibroblast growth factor 19, which accumulates during cholestasis, is also considered as CYP7A1 inhibitor [10].

Table 3. **Lipid metabolism impairment in patients with various internal diseases**

	Changes of lipid fractions			The pathogenesis of the observed phenomena
	TG	LDL	HDL	
Infectious diseases				
COVID-19	↑	↑	↓	The exact mechanism is unclear
AIDS	↑	↓	↓	Decreased TG clearance
Endocrine and metabolic disorders				
Obesity	↑	↑	↓	The secretion of VLDL cholesterol is stimulated, lipolysis of chylomicrons is inhibited. The exchange of cholesterol and triglyceride esters between HDL cholesterol, VLDL cholesterol and LDL cholesterol is activated
Anorexia nervosa	↑	↑	↑	Changes in the intestinal microbiota, resulting in increased absorption of fats and decreased concentration of thyroid hormones.
Type 2 DM	↑↑	↑	↓	Insulin resistance, glycation of apolipoproteins that impairs their metabolism. Activation of the cholesteryl ester transfer protein (CETP).
Type 1 DM	↓	↓	↑ or within reference values	Activation of lipoprotein lipase (LPL) in skeletal muscles and adipose tissue that intensifies VLDL cholesterol catabolism, regulatory effects of insulin.
Hypothyroidism	↑	↑↑		Impaired bile acids synthesis. Deceleration of the hepatic cholesterol uptake from the bloodstream. The number of LDL cholesterol receptors decreases that increases the time of their circulation. Decreased LPL activity.
Cushing's syndrome	↑	↑		Appetite stimulation. Inducing effect on the liver lipogenesis that increases the level of VLDL cholesterol. LPL activation resulting in the increase of fatty acids plasma concentration.
Polycystic ovary syndrome	↑	↑	↓	Metabolic syndrome.
Diseases of the gastrointestinal tract				
Non-alcoholic fatty liver disease (NAFLD)	↑↑	↑	↓	Imbalance between lipid absorption and excretion due to insulin resistance.
Cholestasis		↑↑↑		Inhibition of the conversion of cholesterol to bile acids.
Kidney diseases				
Nephrotic syndrome	↑↑	↑↑	↓	Increased hepatic lipogenesis. Decreased number of LDL cholesterol receptors and LPL activity.
Chronic kidney disease (CKD), stages 3–5	↑	↑	↓	A sharp decline of LDL cholesterol catabolism. Changes correlate with the decrease glomerular filtration rate.
Chronic renal failure	↑	↑↑	↓	
Hematologic diseases				
Paraproteinemia		↑		The affinity of paraproteins to blood plasma lipids that which makes them insensitive to the action of LPL.
Systemic diseases				
Systemic lupus erythematosus (SLE)	↑	↑	↓	Metabolic syndrome. Suppression of lipoprotein lipase. Elevation of C-reactive protein, which binds to lipoproteins and depresses their metabolism.
Rheumatoid arthritis	↑	↑	↓	The pathogenesis is similar to systemic lupus erythematosus.
Psoriasis	↑	↑	↓	Insulin resistance.

Nephrotic syndrome/ chronic kidney disease

Kidney diseases are often associated with lipid metabolism disorders. Patients with nephrotic syndrome have low lipid catabolism due to impaired synthesis of proteins that affect lipoprotein lipase activity (GPIHBP1, ANGPTL4), and increased hepatic lipid synthesis [10]. The main factors that affect lipogenesis in patients with nephrotic syndrome include: changes in plasma albumin concentration, plasma oncotic pressure, local viscosity of the liver sinusoid, loss of urine proteins or other liporegulatory substances.

Patients with 1–2 stage of CKD usually have DLM characterized by the increase of triglycerides, decreased HDL cholesterol. Total cholesterol and LDL cholesterol stay unaltered at these stages of the disease [7].

Systemic lupus erythematosus

The prevalence of dyslipidemia with increased total cholesterol, triglycerides and ApoB-containing lipoproteins (VLDL cholesterol and LDL cholesterol), as well as decreased HDL cholesterol is about 30 % at the initial stage of the disease, and it increases up to 60 % in 3 years [37]. Active stage of systemic lupus erythematosus is usually characterized by the increase of triglycerides and the decrease of HDL cholesterol. Their paraments improve during treatment, while total cholesterol and LDL cholesterol levels remain elevated.

Rheumatoid arthritis

The main cause of premature mortality in patients with rheumatoid arthritis (RA) is atherosclerosis and

its complications. Atherosclerosis develops due to the presence of many traditional risk factors (obesity, arterial hypertension, carbohydrate metabolism disorders, hypodynamia) in these patients [35], stimulated by anti-inflammatory therapy and high inflammatory activity in RA. The severity of lipid disorders correlates with the intensity of arthritis and are most pronounced in systemic RA.

DLM often develops at the onset of the disease in young patients and children, before the prescription of glucocorticoids (see table 3). Moreover, secondary DLM in those with early development of RA can extend to adulthood and, therefore, shorten the duration and affects the quality of life in such patients. DLM is caused by inflammation that affects enzyme activity (increases the action of hepatic lipase, lipid-transfer proteins), induces the increase of serum phospholipase A2 and sphingolipids, and the accumulation of serum amyloid A.

Radiation injury

It is usually thought that radiation can induce the development of atherogenic dyslipidemia that can be explained by the impairment of forward and reverse lipid transport [8].

Pregnancy

Physiological conditions can also cause hyperlipidemia. Thus, all lipid fractions increase during pregnancy [30]. Lipid anabolism predominate during first two trimesters of pregnancy, as the women's organism prepares to increase fetus energy that will be required at the final stage of pregnancy. Insulin sensitivity decreases, which induces lipolysis and decreases the activity of lipoprotein lipase and leads to hypertriglyceridemia during the third trimester. In addition, placental lactogen stimulate lipolysis [10, 30].

Conclusion

This review article analyzed wide range of secondary hyperlipidemia. The main factor that decreases cardiovascular risk is the achievement of target blood lipids levels, therefore, modern diagnostics should focus on timely detection and correction of lipid metabolism disorders.

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