Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

The Physiological Aspects Of Hyperlipidemia In Health And Disease

Ali Ibrahim Ali AL-Ezzy[1] ,Marah Salim Hameed[2]

Department of pathology, College of Veterinary Medicine, University of Diyala, Iraq
Department of physiology &pharmacology , College of Veterinary Medicine, University of Diyala, Iraq

Corresponding author : alizziibrahim@gmail.com

Received: 1 -4-2021 **Accepted: 20-5-2021** **Published: 1-7-2021**

Abstract

Hyperlipidemia is abnormally elevated levels of any or all lipid or lipoproteins in the blood due to abnormal fat metabolism or function . Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters and phospholipids and or plasma lipoproteins including very low density lipoprotein and low-density lipoprotein, and reduced high-density lipoprotein levels. The high-density lipoprotein is a major protective factor that helps in obliterating cholesterol from the arterial wall. The ratio of high-density lipoprotein and total cholesterol is a prevalent way to assess the atherogenicity index . Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases in animals and human .

Keywords : Hyperlipidemia, Risk factors, Etiology, physiology and pathophysiology

How to cite the article:
AL-Ezzy, A. I. A. and M. S. Hameed (2021). "The physiological Aspects of Hyperlipidemia in Health and Disease " Diyala Journal For Veterinary Sciences 1(2): 1-9.

Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

Introduction

Hyperlipidemia is abnormally elevated levels of any or all lipid or lipoproteins in the blood due to abnormal fat metabolism or function [4]. Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters ; phospholipids and or plasma lipoproteins including very low density lipoprotein , low-density lipoprotein, and reduced high-density lipoprotein levels[5] . Hyperlipidemia is a metabolic disorder occurring in serum lipid and lipoproteins profile due to quantitative increase in the net level of low density lipoprotein cholesterol , very low density lipoproteins , total cholesterol ,triglycerides , with a collateral decrease in the concentrations of high density lipoproteins in the blood circulation[3].The high-density lipoprotein is a major protective factor that helps in obliterating cholesterol from the arterial wall. The ratio of high-density lipoprotein and total cholesterol is a prevalent way to assess the atherogenicity index; a Ratio of more than 4.5 is atherogenic[6].

Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD) [7, 8] . There is a strong relation between IHD and the high mortality rate. Furthermore elevated plasma cholesterol levels cause more than four million deaths in a year[9, 10]. Atherosclerosis is a process of arteries hardening due to deposition of cholesterol in the arterial wall which causes narrowing of the arteries. Atherosclerosis and atherosclerosis associated disorders like coronary, cerebrovascular and peripheral vascular diseases are accelerated by the presence of hyperlipidemia[11] .

Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases [3, 5] .

Over oxidative stress and free radicals attack and induce oxidative damage to various biomolecules including proteins, lipids, lipoproteins, and DNA [12, 13] .Some natural anti-oxidants like catalase, superperoxide dismutase, Glutathione peroxidase, Heme-oxygenase act as radical scavengers constitute the repair systems for biomolecules damaged by the attack of free radicals [14].In many cases, hyperlipidemia is caused by the overingestion of a diet rich in cholesterol, alcohol attention is also being paid to treat the patients with hyperlipidemia using strict dietary management and appropriate excerise[3, 15].The main aim of treatment in patients with hyperlipidemia is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular or cerebrovascular diseases [16] .

"Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins[17]

The aim of current review is to describe the physiological aspects of hyperlipidemia in health and disease .

Plasma lipoproteins

Composition

Lipoproteins are macro molecules aggregate composed of lipids and proteins; this structure facilitates lipids compatibility with the aqueous body fluids. Lipoproteins composed from nonpolar lipids (triglycerides and cholesteryl esters),polar lipids(phospholipids and unesterified cholesterol) and specific proteins known as apolipoproteins. Apolipoproteins are amphiphilic proteins that bind to both lipids and the plasma [18]

Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

Classification

[1] Chylomicrons: Large particles that carry dietary fat (mainly TG) from the intestine to the liver

[2] Very low density lipoprotein (VLDL): Carries endogenous TG synthesized in the liver to the tissues

[3] Low density lipoprotein (LDL): Formed from intermediate density lipoprotein (IDL) by hepatic lipase It carries cholesterol from liver to tissues

[4] High density lipoprotein (HDL): Carries cholesterol from tissues to liver .

Function

Plasma lipoproteins are important for lipid solubilization in order to transport triglycerides, an Important energy source, which synthesized and absorbed to places of utilization and storage; and to transport cholesterol between different places of absorption, synthesis, catabolism, and elimination[19]

Etiology and classification of hyperlipidemia

Hyperlipidemia general can be classified to:

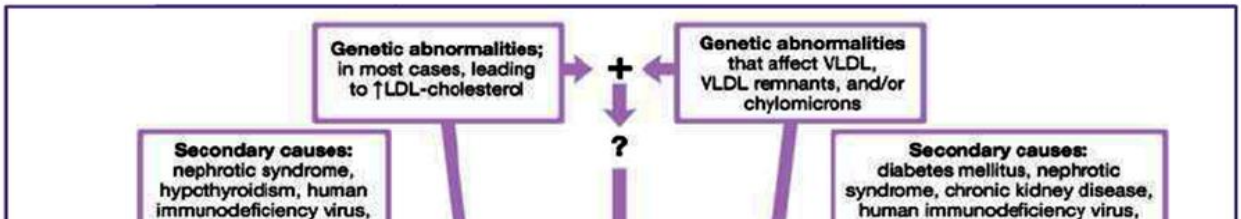
[1] **Primary:** it is also called familial due to a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects. Primary hyperlipidemia can usually be resolved in to one of the abnormal lipoprotein patterns summarized in table (1) and figure(1) .

[2] **Secondary:** it is acquired because it is caused by another disorder like diabetes, nephritic syndrome, chronic alcoholism, hypothyroidism and with use of drugs like corticosteroids, beta blockers and oral contraceptives. Corticosteroids, anabolic steroids, Isotretinoin , thiazide diuretics ,anticonvulsants, beta blockers, estrogen, anti-retrovirals, obesity, ketogenic diets

The main cause of hyperlipidemia includes changes in lifestyle habits in which risk factor is mainly poor diet in which fat intake form saturated fat and cholesterol exceeds 40 percent of the total calories uptake[20] .

Table. 1: Fredrickson classification of primary hyperlipidemia [1]

Type	Disorder	Cause	Occurrence	Elevated plasma lipoprotein
I	Familial hyperchylomicronemiaOr Primary hyperlipoproteinemia	Lipoprotein lipase deficiencyor Altered ApoC2	Very rare	Chylomicrons
IIa	Familial hypercholesterolemia OrPolygenic hypercholesterolemia	LDL receptor deficiency	Less common	LDL
IIb	Familial combined hyperlipidemia	Decreased LDL receptor	Commonest	LDL and VLDL
III	Familial dysbetalipoprotenemia	Defect in Apo E- 2 synthesis and increased ApoB	Rare	IDL
IV	Familial hypertriglyceridemia	Increased VLDL production and decreased excretion	common	LDL
V	Endogenous hypertriglyceridemia	Increased VLDL production and decreased LPL	Less common	VLDL and chylomicrons



Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

Risk Factors for Hyperlipidemia

Risk Factors for Hyperlipidemia was illustrated in table (2) according to [3] .Overproduction and defective clearance of the cholesterol, TG and LDL is the result of the mutations of single or multiple genes. This is called non modifiable Risk Factors.

It is also known as primary causes The primary disorders are the common dyslipidemia causes to the children, although it may not affect in the most cases of adult dyslipidemia .

Non modifiable risk factors

Age, Gender and Genetic:

Although unhealthy lifestyle choices are the main cause of hyperlipidemia, patient can also inherit it[21]. Once a man reaches age 45 and a women reaches age 55, the risk naturally goes up due to age-related changes in the body [2].With age, the heart muscle doesn't work as well as it once did. This can increase pressure on arteries . For women it happens later, after they go through menopause and their cholesterol levels tend to rise. Post-menopausal female have elevated levels of total cholesterol, LDL-C, and apolipoprotein B as compared with premenopausal women. Total HDL decreases in postmenopausal women. Although there is nothing people can do about age or genetic makeup, this does not mean the condition cannot be controlled [22]

Chronic Diseases :

Chronic diseases that make the cardiovascular system work harder can also cause high cholesterol levels. If the test positive for high cholesterol and the cause is not obvious ,the physician may look for an underlying disease. This includes kidney problems and liver disease, conditions that affect your thyroid, a malfunction of the pituitary gland, and diabetes [23] . In many cases, when these

Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

conditions are controlled, cholesterol levels improve. High blood sugar contributes to higher LDL cholesterol and lower HDL cholesterol [24] . High blood sugar also damages the lining of the arteries. Other cholestatic liver diseases and primary biliary cirrhosis increase the risk of dislipidemia [25]

Modifiable risk factors

Medications:

Drugs like thiazides, retinoids,estrogens and glucocorticoids, among others also increase the risk of dislipidemia

Nutrition :

Unhealthy diet raises the risk for hyperlipidemia in two ways. First is what the diet is made up of[26]. Eating high amounts fat and cholesterol contribute to higher lipid levels in the blood. In addition, consuming more calories leads to the excess calories being stored in the body as fat [27]. According to the National Cholesterol Education Program (NCEP), losing weight and eating healthy lowers the bad cholesterol that gets stored in the body and raises the good kind of cholesterol that tends to be excreted from the body [2]

Physical inactivity:

Being active also tends to lower the bad cholesterol numbers and raise the good. Physical inactivity can lead to weight gain. This is why physical inactivity is also considered a risk factor for hyperlipidemia [16]. Cigarette smoking damages the walls of the blood vessels, making them likely to accumulate fatty deposits. Smoking may also lower your level of HDL [12,13]. The risk increases if the patient is a man with a waist circumference of at least (102 cm) or a woman with a waist circumference of at least (89 cm) [16] . Fig. 1 elaborates the interaction between causes .

Table(2) Risk Factors for Hyperlipidemia [3]

Exogenous	Corticosteroids, anabolic steroids, isotretinoin, thiazide diuretics anticonvulsants, beta blockers, estrogen, anti-retrovirals, Alcohol, obesity, ketogenic diets
Endocrine	Hypothyrodism, Cushing syndrome, Hypopituitarism, Diabetes mellitus, Lipodystrophy
Storage diseases	Glycogen storage diseases, Gaucher disease, Cystine storage, Tay-Sachs disease, Neumann-Pick disease, Acute intermittent porphyria
Gastrointestinal	Cholestasis, Hepatitis, Cirrhosis, Pancreatitis
Renal	Nephrotic syndrome, Renal failure, Hemolytic uremic syndrome, Anorexia nervosa
other factors	Malnutrition, Anorexia nervosa, Idiopathic hypercalcemia, Progeria, Systemic lupus erythematous

Pathogenesis of hyperlipidemia

Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

Fatty acid synthesis initiates with acetyl-CoA and throughout addition of two-carbon atoms. Fatty acid synthesis occurs in the cells cytoplasm, while Fatty acid oxidation occurs in the mitochondria. The main sites of fatty acid synthesis are the liver and adipose tissue. Hyperlipemia happens when adipose lipolysis (HSL-dependent and ATGL-) and consequent hepatic VLDL synthesis (substrate-dependent and MTP-) exceeds the rate of clearance of plasma VLDL (LPL- and VLDL receptor dependent) .Hyperlipidemia is promoted by a sedentary lifestyle and unhealthy diet in environmentally and genetically predisposed people. Impaired adiposeness of subcutaneous, peripheral lipids tissue during positive caloric balance may increase lipids deposited in non-adipose tissue organs such as muscle, liver, and pancreas causing lipotoxicity. Adiposopathic endocrine is directly pathogenic to the cardiovascular system and other body. Adiposopathy is indirectly promote other atherosclerotic risk factors such as high blood pressure, type 2 diabetes mellitus [28].

Symptoms of hyperlipidemia: Generally hyperlipidemia does not have any obvious symptoms but they are usually discovered during routine examination or until it reaches the danger stage of a stroke or heart attack .Patients with high blood cholesterol level or patients with the familial forms of the disorder can develop xanthomas which are deposits of cholesterol may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their body[1, 29].Hyperlipidemia symptoms may include:"

Symptoms of peripheral artery disease (PAD), including[30]:

a) Leg discomfort.

b) Leg pain or cramping that occurs when walking and is relieved at rest (intermittent claudication) .

c) Pain in the ball of the foot or toes, while at rest, as PAD progresses .

d) In more severe forms, painful foot ulcers, blue or black discoloration of the toes, infections, and gangrene .

Symptoms of a transient ischemic attack (TIA) or stroke, including[31, 32] :

a) Sudden, severe headache.

b) Weakness, numbness, or tingling on one side of your body (one arm and/or leg).

c) Loss of movement of one arm or leg.

d) Partial vision loss in one eye (often described as pulling down a window shade) .

e) Inability to speak clearly or express your thoughts .

Symptoms of a heart attack, including[33]:

a) Chest pain, which may feel like pressure or squeezing in your chest .

b) Pain or pressure in your shoulders, arms, neck, jaw, or back .

c) Shortness of breath.

Angina: Chest pain that happens when your heart muscle can't get enough oxygen[34]

Atherosclerosis :

Hyperlipidemia is the most important risk factor for atherosclerosis, which is the major cause of cardiovascular disease. Atherosclerosisis a pathologic process characterized by the accumulation of lipids, cholesterol and calcium and the development of fibrous plaques within the walls of large and medium arteries [35]

Complications Of Hyperlipidemia:

Diyala Journal for Veterinary sciences
Open Access Journal Published by College of Veterinary Medicine
University of Diyala, Iraq
P-ISSN: 2410-8863
Vol. 1, NO. 2, June 2021
Proceedings of 2nd National & 1st International Scientific Conference
Of Veterinary Medicine & Science , (NISCVMS-2021)

Coronary Artery Disease (CAD):

Atherosclerosis, the major cause of coronary artery disease, characterized by the accumulation of lipid and the formation of fibrous plaques within the wall of the arteries resulting in narrowing of the arteries that supply blood to the myocardium, and results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart. Elevated lipid profile has been connected to the development of coronary atherosclerosis [36] .

Myocardial Infarction (MI):

MI is a condition which occurs when blood and oxygen supplies are partially or completely blocked from flowing in one or more cardiac arteries, resulting in damage or death of heart cells. The occlusion may be due to ruptured atherosclerotic plaque. The studies show that about one-fourth of survivors of myocardial infarction were hyperlipidemic [37] .

Ischemic stroke:

stroke is the fourth leading cause of death. Usually strokes occur due to blockage of an artery by a blood clot or a piece of atherosclerotic plaque that breaks loose in a small vessel within the brain. Many clinical trials revealed that lowering of low-density lipoprotein and total cholesterol by 15% significantly reduced the risk of the first stroke[38].

References

[1]. Tripathi K. Essentials of Medical Pharmacology. 5 [sup] th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. 2008:778-9.

[2]. Nouh F, Omar M, Younis M. Risk Factors and Management of Hyperlipidemia. Asian Journal of Cardiology Research. 2019:1-10.

[3]. Nagarthna P, Bashir B, Sridhar K. Hyperlipidemia And Its Treatment: A Review. Journal of Advanced Scientific Research. 2020;11(1).

[4]. Yao YS, Di Li T, Zeng ZH. Mechanisms underlying direct actions of hyperlipidemia on myocardium: an updated review. Lipids in Health and Disease. 2020;19(1):1-6.

[5]. Mishra PR, Panda PK, Apanna K, Panigrahi S. Evaluation of acute hypolipidemic activity of different plant extracts in Triton WR-1339 induced hyperlipidemia in albino rats. Pharmacologyonline. 2011;3:925-34.

[6]. Choudhary MK, Eräranta A, Koskela J, Tikkakoski AJ, Nevalainen PI, Kähönen M, *et al.* Atherogenic index of plasma is related to arterial stiffness but not to blood pressure in normotensive and never-treated hypertensive subjects. Blood pressure. 2019;28(3):157-67.

[7]. Brouwers MC, Van Greevenbroek MM, Stehouwer CD, De Graaf J, Stalenhoef AF. The genetics of familial combined hyperlipidaemia. Nature reviews endocrinology. 2012;8(6):352.

[8]. Lu T, Forgetta V, Oriana H, Mokry L, Gregory M, Thanassoulis G, *et al.* Polygenic risk for coronary heart disease acts through atherosclerosis in type 2 diabetes. Cardiovascular Diabetology. 2020;19(1):12.

[9]. Kumar D, Parcha V, Maithani A, Dhulia I. Effect and evaluation of antihyperlipidemic activity guided isolated fraction from total methanol extract of Bauhinia variegata (linn.) in Triton WR–1339 induced hyperlipidemic rats. Asian Pacific Journal of Tropical Disease. 2012;2:S909-S13.

[10]. Shahid SU, Rehman A. Predictive value of plasma lipid levels for coronary artery disease (CAD). Biologia. 2020:1-9.

[11]. Kaski JC, Kjeldsen KP. The ESC Handbook on Cardiovascular

Pharmacotherapy: Oxford University Press; 2019.

[12]. Maddu N. Diseases Related to Types of Free Radicals. Antioxidants: IntechOpen; 2019.

[13]. Bhattacharjee S. ROS and Oxidative Modification of Cellular Components. Reactive Oxygen Species in Plant Biology: Springer; 2019. p. 81-105.

[14]. Palmieri B, Sblendorio V. Oxidative stress tests: overview on reliability and use. European review for medical and pharmacological sciences. 2007;11(6):383-99.

[15]. Sikarwar Mukesh S, Patil M. Antihyperlipidemic effect of ethanolic extract of Hibiscus rosa sinensis flowers in hyperlipidemic rats. RGUHS J Pharm Sci. 2011;1(2):117-22.

[16]. Mohsen MM, Riad NA, Badawy AI, El-Hammed BMA, Elsherbini DMAE. Effectiveness of Life Style Modification on Lipid Profile for Patients with Hyperlipidemia. American Journal of Nursing. 2020;9(1):8-18.

[17]. Rizzo M, Kotur-Stevuljevic J, Berneis K, Spinas G, Rini GB, Jelic-Ivanovic Z, *et al.* Atherogenic dyslipidemia and oxidative stress: a new look. Translational Research. 2009;153(5):217-23.

[18]. Rodes J, Benhamou J-P, Blei A, Reichen J, Rizzetto M. Textbook of hepatology: from basic science to clinical practice: Blackwell Malden, MA; 2007.

[19]. Ferrier DR. Biochemistry: Lippincott Williams & Wilkins; 2014.

[20]. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A Pathophysiologic Approach, ed: McGraw-Hill Medical, New York; 2014.

[21]. Papaioannou I, Lampropoulos CE, Panagiotakos DB, Skoumas J, Pitsavos CH, Tousoulis D. Prognostic value of exercise tolerance test for predicting cardiovascular disease in asymptomatic individuals with heterozygous familiar hypercholesterolemia. Heart and Vessels. 2020;35(2):259-67.

[22]. Saadi H, Carruthers SG, Nagelkerke N, Al-Maskari F, Afandi B, Reed R, *et al.* Prevalence of diabetes mellitus and its complications in a population-based sample in Al Ain, United Arab Emirates. Diabetes research and clinical practice. 2007;78(3):369-77.

[23]. Tomlinson B, Chan P, Lam CWK. Postprandial hyperlipidemia as a risk factor in patients with type 2 diabetes. Expert Review of Endocrinology & Metabolism. 2020(just-accepted).

[24]. Lazarte J, Hegele RA. Dyslipidemia management in adults with diabetes. Canadian journal of diabetes. 2020;44(1):53-60.

[25]. Pedersen MR, Mayo MJ. Managing the symptoms and Complications of Cholestasis. Clinical Liver Disease. 2020;15(3):120.

[26]. Shree R, Ghosh AK, Bharti SK. Effect of dietary Withenia somnifera and Commiphora weightii on induced hyperlipidemic wistar rats. 2020.

[27]. Nair KP. Overweight and Obesity: The Bane of Modern Times. Food and Human Responses: Springer; 2020. p. 173-203.

[28]. Al-Moosa S, Allin S, Jemiai N, Al-Lawati J, Mossialos E. Diabetes and urbanization in the Omani population: an analysis of national survey data. Population health metrics. 2006;4(1):5.

[29]. Karam I, Ma N, Liu X, Li J, Yang Y. Short Review on Hyperlipidemia. J Blood Transfusions Dis. 2019;2(2):86-8.

[30]. Olin JW, Sealove BA, editors. Peripheral artery disease: current insight into the disease and its diagnosis and management. Mayo Clinic Proceedings; 2010: Elsevier.

[31]. Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJ. Early risk of stroke after a transient ischemic attack in

patients with internal carotid artery disease. Cmaj. 2004;170(7):1105-9.

[32]. Ay H, Koroshetz WJ, Benner T, Vangel MG, Wu O, Schwamm LH, *et al.*, editors. Transient ischemic attack with infarction: a unique syndrome? International Congress Series; 2006: Elsevier.

[33]. Harikumar K, Ramunaik M, Suvarna C. A review on hyperlipidemic. International Journal of Novel Trends in Pharmaceutical Sciences. 2013;3(4):59-71.

[34]. Ogura M, Makino H, Kamiya C, Yoshimatsu J, Soran H, Eatough R, *et al.* Lipoprotein apheresis is essential for managing pregnancies in patients with homozygous familial hypercholesterolemia: seven case series and discussion. Atherosclerosis. 2016;254:179-83.

[35]. Wouters K, Shiri-Sverdlov R, van Gorp PJ, van Bilsen M, Hofker MH. Understanding hyperlipidemia and atherosclerosis: lessons from genetically modified apoe and ldlr mice. Clinical Chemistry and Laboratory Medicine (CCLM). 2005;43(5):470-9.

[36]. Gao W, He H-W, Wang Z-M, Zhao H, Lian X-Q, Wang Y-S, *et al.* Plasma levels of lipometabolism-related miR-122 and miR-370 are increased in patients with hyperlipidemia and associated with coronary artery disease. Lipids in health and disease. 2012;11(1):55.

[37]. Gulati R, Behfar A, Narula J, Kanwar A, Lerman A, Cooper L, *et al.*, editors. Acute Myocardial Infarction in Young Individuals. Mayo Clinic Proceedings; 2020: Elsevier.

[38]. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. The Lancet Neurology. 2009;8(5):453-63.