

Chapter 01

Cardiovascular Risk Factors in Adolescence. Clinical Epidemiology and Early Prevention (English Version)
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Clinical and Epidemiological Foundations of Cardiovascular Risk in Adolescence

Fundamentos clínicos y epidemiológicos del riesgo cardiovascular en la adolescencia

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Chronic noncommunicable diseases (CNCDs) are the leading cause of death worldwide, accounting for 38 million (68 %) of the 56 million deaths recorded each year. Nearly three-quarters of all NCD deaths (28 million) and most premature deaths (82 %) occurred in low- and middle-income countries.⁽¹⁾

Cardiovascular disease (CVD) affects the heart and blood vessels, with ischemic heart disease and cerebrovascular disease being the most prevalent clinical forms of this public health problem. In cardiovascular disease, atherosclerosis is the pathophysiological mechanism, and cardiovascular risk factors contribute decisively to the onset of this disorder.⁽²⁾

CVD is the leading cause of death from NCDs and is responsible for 17,5 million deaths, or 46 % of NCD deaths. Among these deaths, an estimated 7,4 million were due to heart attack (ischemic heart disease), and 6,7 million were due to stroke.^(1,3)

To accelerate national action to address NCDs, in 2013, the World Health Organization adopted nine specific global targets for 2025 and approved a set of actions organized around the World Health Organization (WHO) Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020. Among the proposed objectives is “Global Target 6,” which proposes a “25 % relative reduction in the prevalence of hypertension, or containment of the prevalence of hypertension, depending on country circumstances, by 2025.”⁽¹⁾

Similarly, in 2015, world leaders adopted a set of global goals to eradicate poverty, protect the planet, and ensure prosperity for all as part of a new sustainable development agenda. Among the goals set in the field of health are “By 2030, reduce premature mortality from noncommunicable diseases by one-third through prevention and treatment and promote mental health and well-being.”⁽⁴⁾

In this global context, Latin America is undergoing an epidemiological transition, with the coexistence of acute infectious diseases and chronic cardiovascular diseases. Cardiovascular mortality accounts for 26 % of all deaths but could increase due to the increasing prevalence of risk factors.^(1,5)

Cardiovascular risk (CVR) is the probability of suffering a cardiovascular event within a given period of time (usually 5-10 years). Quantifying this risk, especially in patients who do not have the disease, is essential for determining the intensity of intervention and the need for drug treatment.^(6,7) In this sense, a cardiovascular risk factor is a biological characteristic, condition, and/or behavior that increases the probability of suffering from or dying from cardiovascular

disease.⁽⁸⁾ Cardiovascular risk factors are divided into two main groups: modifiable or controllable (smoking, sedentary lifestyle, obesity, diabetes, high blood pressure, and dyslipidemia) and nonmodifiable (skin color, sex, age, and family history).⁽⁹⁾

From an academic point of view, the term CVRF has two meanings, one more generally, to indicate any condition related to the risk of developing one of the most common CVDs: ischemic heart disease, atherothrombotic vascular accidents, renal artery atheromatosis, atherothrombotic processes, central retinal artery thrombosis, and intermittent claudication. The other, more specific meaning usually refers to coronary risk, designating certain biological signs, lifestyles, or acquired habits that are more prevalent among candidates for future coronary heart disease.^(10,11)

Some CVRFs, such as high BP, high TC, and low HDL cholesterol, can worsen atherosclerotic lesions and increase the incidence of CVD.⁽¹²⁾

The relationship between lipids and atherosclerosis has been widely supported by numerous studies.^(12,13,14) The presence of cholesterol in atherosclerotic plaques and the experimental triggering of atherosclerosis by feeding animals a high-cholesterol diet are well known. In addition, numerous observational and interventional studies in adults have been conducted, corroborating the experimental findings. Arterial hypertension (AHT) is one of the most important CVRFs, and in terms of its impact, it can be placed immediately behind hypercholesterolemia and ahead of smoking.^(15,16,17)

Various epidemiological studies conducted in adults have demonstrated the predictive value of SAH for CVRF and total mortality. However, the Framingham study has shown that SAH is a more accurate predictor of stroke than peripheral artery disease or ischemic heart disease.^(6,18)

Recent studies have concluded that isolated systolic hypertension is a major risk factor and should always be treated; other studies attach enormous predictive value to ambulatory blood pressure (BP) monitoring as a predictor of risk in hypertensive patients.^(19,20)

The prevalence of hypertension increases in all population groups as age increases, although the black population may have more severe forms of hypertension than the white population does, with a higher prevalence in this population. The prevalence in childhood is not well established, but it is estimated to range from 0,6 % to 11 % in American children and adolescents.^(21,22,23)

In the Americas, only three countries have population-level control of hypertension above 35 % (Cuba, the United States of America, and Canada), which is the commitment adopted by the Member States of the Pan American Health Organization for 2019.^(24,25,26,27,28)

Health priorities, available resources, socioeconomic conditions of the population, and the epidemiology of hypertension and related diseases vary considerably between countries and even between regions within the same country.^(29,30,31,32,33) According to a seven-country study, the linear association between BP and risk is parallel in different countries, confirming that BP always explains a variation in relative risk, but absolute risk, a key parameter for defining decision thresholds, differs by a factor of one to five among the populations studied, supporting different diagnostic and therapeutic approaches.^(26,27)

In Cuba, various projects are being developed to reduce the risk of cardiovascular disease;

their main purpose is to improve the level of control of high blood pressure. Numerous examples demonstrate the results achieved by these actions.^(28,29) In 1998 and 2010, Cuba carried out national campaigns to improve the control of high blood pressure. The detection of hypertensive individuals aged 15 years or older registered in health services increased from 8,8 % in 1996 to 12,5 % in 1998, increasing to 25 % in 2015.^(34,35,36) These results were corroborated in the Third National Survey of Risk Factors and Preventive Activities for Noncommunicable Diseases, as 73 % of hypertensive individuals were aware of their condition, 89 % of those who were aware of their disease received treatment, and 55 % managed to control their hypertension; at the population level, hypertension control was 36 %.^(24,37,38,39)

Castillo Herreral et al.⁽⁴⁰⁾ argued that the detection, diagnosis, and treatment of primary hypertension and its risk factors in early life is a health problem of unquestionable value and importance, with the goal of reducing the prevalence and complications of this disease in adulthood.

In our country, the prevalence of hypertension in children is not known precisely; however, the prevalence of primary hypertension has been estimated to be 4,7 %, and the prevalence of prehypertension is 9,7 %.⁽³¹⁾

The reasons for considering the prevention of coronary heart disease during childhood and adolescence are based, first, on evidence from the pathological anatomy of atherosclerosis in humans. In the second decade of life, fatty deposits form in the arteries, which can subsequently progress to fibrous plaques in the third decade of life and to more complicated lesions in the fourth decade and in older individuals.⁽¹¹⁾

Second, they also depend on epidemiological evidence regarding the early development of the main risk factors, blood cholesterol and hypertension, and their relationship with the development of early lesions in the aorta and coronary arteries of adolescents, which have been sufficiently proven. All of the above findings suggest that the prevention of CVD should begin in early life. Both pieces of evidence indicate that action prior to maturity is required for the complete prevention of arteriosclerosis. Those most at risk of developing hypertension in adulthood are those with higher BP readings at an earlier age.^(22,32)

The imprecise differences between BP and cholesterol levels in childhood and adolescence in relation to the results obtained in other countries, apart from the methodological problems of the different studies,^(15,33,34,35,36,37) suggest that population studies should be conducted in situ.

Knowing the cardiovascular risk factors in the adolescent population being treated will make it possible to identify those individuals most vulnerable to developing cardiovascular disease, apply preventive measures, and take early action, particularly in relation to modifiable factors.

Cardiovascular and cerebrovascular diseases

Vascular and brain diseases are the third leading cause of death in Cuba and worldwide, with a tendency to become the second leading cause as the population ages.⁽²⁸⁾

Although cardiovascular disease usually manifests itself in adulthood, the pathological process and risk habits that eventually lead to the disease begin in childhood and adolescence. Arterial damage begins with small deposits of fat, often early in life.⁽⁷⁾

Autopsies of young people and young adults who died from accidents or other noncardiovascular

causes revealed premature fatty deposits in the arteries. These changes correlate with traditional risk factors for cardiovascular disease. These fatty deposits can progress to larger lesions, which can progressively occlude the lumen of the artery.⁽¹⁰⁾

Its etiology is multifactorial, but most cases are due to exogenous factors (75 %), with genetic factors accounting for only approximately 25 % of the etiology. Risk factors include behavioral (diet, physical activity, tobacco, alcohol), biological (dyslipidemia, hypertension, overweight), and social (socioeconomic, cultural) factors. Behavioral risk factors are responsible for 75 % of cardiovascular diseases.^(16,17)

Other classifications include modifiable and nonmodifiable risk factors. Modifiable risk factors include smoking, high blood pressure, hypercholesterolemia, diabetes mellitus, hypertriglyceridemia, and obesity. Nonmodifiable risk factors include age, male sex, black or Asian race, and family history of cardiovascular disease.⁽¹⁹⁾

The risk factors for cardiovascular disease are synergistic and include the following:

Smoking: smokers have significantly higher concentrations of cholesterol, triglycerides, and LDL. Smoking is associated with a higher incidence of acute myocardial infarction and coronary heart disease. Studies indicate that even passive exposure to cigarette smoke is a major cause of cardiovascular mortality.^(5,7)

Dyslipidemia refers to high LDL levels, low HDL levels, hypercholesterolemia, and hypertriglyceridemia. As a risk factor, it has a strong dose–response relationship. Although lipid metabolism is determined by genetic factors, the daily consumption of cholesterol, saturated fat, and trans fatty acids increases cholesterol levels.⁽⁹⁾

Hypertension is considered a cardiovascular disease and a risk factor for cardiovascular disease. Systolic pressure is most closely related to cardiovascular disease, especially in elderly individuals. However, some studies have focused more on pulse pressure and diastolic pressure. Hypertension has been found to improve with lifestyle changes such as diet (fruit, low salt, and alcohol), weight loss, and exercise.^(5,8,9)

Sedentary lifestyle is considered one of the four major risk factors for cardiovascular disease. Physical activity improves insulin resistance and blood pressure, increases HDL levels, lowers triglyceride levels, and promotes fibrinolysis. Medical guidelines recommend at least 30 minutes of walking as physical activity.⁽³⁸⁾

Diabetes mellitus is considered a major risk factor for cardiovascular disease, and many patients with cardiovascular disease also have diabetes mellitus. Currently, many specialists consider diabetes mellitus to be a cardiovascular disease. Type II diabetes mellitus represents twice the risk for men and four times the risk for women. In addition, diabetes mellitus is accompanied by other risk factors, such as insulin resistance and dyslipidemia. It has been proven that diabetes mellitus improves with diet and exercise.⁽¹⁶⁾

Obesity is a major risk factor for cardiovascular disease. Although BMI is often used to estimate obesity, central obesity is considered a greater predictor of CVD. The increase in obesity is attributed to several factors, such as car use, television, the internet, a decrease in physical activity programs in schools, fast food, and larger food portions. Obesity is a risk factor for other risk factors, such as hypertension, low HDL, insulin resistance, and hypertriglyceridemia.^(16,18)

Hormonal: some studies have demonstrated the protective effect of estrogen against cardiovascular disease. Low estrogen levels are associated with alterations in arterial tone and flow, low HDL levels, and high LDL levels.⁽³⁹⁾

Other dietary factors: there is some evidence that insufficient consumption of fruits and vegetables contributes to cardiovascular disease, especially given the protective effect that antioxidants such as vitamins E and C found in these foods appear to have. Total abstinence from alcohol inhibits the protective effect that drinking a glass of red wine seems to have by increasing HDL, although more benefits have been observed in elderly individuals. Low folic acid intake appears to be related to high homocysteine levels, which are linked to cardiovascular disease, especially coronary heart disease.^(6,9)

Psychosocial factors such as anxiety, depression, hostility, and type A behavior have been linked to a higher incidence of cardiovascular disease. Recently, attention has been given to socioeconomic and cultural status as risk factors for cardiovascular disease, as they are associated with risky behaviors regarding diet and physical activity.⁽⁸⁾

New risk factors have been identified, including alterations in coagulation factors, fibrinogen, factor VII, factor VIII, and platelet aggregation, which promote cardiovascular disease and are genetic in origin. On the other hand, infections have been identified as risk factors for CVD. Among these infections, *Chlamydia pneumoniae* has been found in atherosclerotic plaques, and herpesvirus has been found to stimulate atherosclerosis. Other microorganisms, such as *Helicobacter pylori* and cytomegalovirus, have been linked to CVD, but their mechanism of action is still poorly understood.^(2,11)

Atherosclerosis is known to be the main cause of vascular diseases, and hyperlipidemia, considered one of the most common metabolic diseases, is one of the predominant triggering factors. The first step in its diagnosis is the quantitative determination of baseline cholesterol, triglyceride, and lipoprotein levels in serum or plasma, in addition to a necessary combination of personal and family history, diet, medication, a complete physical examination, and other laboratory tests to define the specific lipid disorder.^(35,40,41)

Interest in hyperlipidemia has increased in recent years as a result of its easy diagnosis and classification and its relationship with atherosclerosis. Its importance as a metabolic disease is surpassed only by that of diabetes mellitus. In recent years, the high frequency of these disorders in the general population has become apparent, not only in the form of hypercholesterolemia but also in those with elevated serum triglycerides.^(42,43,44)

Lipids

Lipids are a group of biomolecules that, unlike proteins and carbohydrates, do not have a repeating structural unit. They are made up of compounds with a wide variety of chemical compositions, but they share the common characteristic of being insoluble in water and soluble in organic solvents such as hexane, methanol, benzene, chloroform, dichloromethane, or a mixture of these, such as chloroform:methanol (2:1).⁽³²⁾

Alterations in lipid metabolism are classified as follows:^(45,46)

1. Alterations in the digestion or absorption of fats, or steatorrhea.
2. Dyslipoproteinaemia or dyslipidemia.
3. Lipoidosis.
4. Alterations in the usual lipid deposits (obesity-thinness-lipodystrophy).

5. Pathology of intermediate lipid metabolism (ketonemia).
6. Disorders of fat elimination.

Lipids perform different types of biological functions:

- Energy reserve function: triglycerides are the main energy reserve in animals.
- Structural function: triglycerides in the adipose tissue coat provide consistency to organs and mechanically protect structures or act as thermal insulators.
- Regulatory, hormonal, or cellular communication functions: water-soluble vitamins are lipidic in nature (terpenoids, steroids); steroid hormones regulate metabolism and reproductive functions; glycolipids act as membrane receptors; and eicosanoids play prominent roles in cellular communication, inflammation, and the immune response.
- Relaxing function: lipids accumulate in adipose tissue, forming large fatty tissues that manifest as weight gain in sedentary individuals, which increases the concentration of TRL hormones in the blood.
- They constitute the structure of the cytoplasmic membrane: phospholipids, glycolipids, and cholesterol form the lipid bilayers of biological membranes.

The human body uses three types of lipid transport vehicles:

- Lipoproteins, such as chylomicrons, transport them to the liver after absorption by the intestine, from which they are distributed to the remaining body's cells, especially fat and muscle cells, in the form of VLDL, IDL, LDL, and HDL lipoproteins. Adipose tissue cells are the main fat storage cells.
- Serum albumin: free fatty acids are transported.
- Ketone bodies: small, water-soluble molecules are produced in the liver by the oxidation of fatty acids. Since they are soluble in water (and therefore in blood), they can travel through it without any problems.

Lipoproteins

The lipid compounds that circulate in the blood are found as part of the various plasma lipoproteins. However, a small fraction of free fatty acids are transported in the blood bound to plasma albumin.⁽⁴⁷⁾

Lipoproteins are complexes of lipids and specific proteins, called apolipoproteins, whose function is to transport lipids in aqueous media such as blood. Apolipoproteins (apos) are proteins that can solubilize lipids in the blood. Apolipoproteins are named according to a letter and a number, ranging from apo A-I to apo M. The main lipids transported by lipoproteins include unesterified cholesterol, esterified cholesterol, triglycerides, and phospholipids as the major components.⁽⁴⁸⁾

In the study of lipoprotein structure, two parts are usually distinguished: the core and the shell. The core contains the most hydrophobic lipids (cholesterol esters and triglycerides), whereas the shell contains the more polar domains of phospholipids and unesterified cholesterol, as well as the more polar domains of apolipoproteins.⁽⁴⁹⁾

We can distinguish five major groups of lipoproteins on the basis of their density: chylomicrons, very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs), which have different sizes and chemical compositions.⁽⁵⁰⁾ The following table describes the composition of lipoproteins:

Table 1. Composition of lipoproteins					
	Qm	VLDL	IDL	LDL	HDL
Diameter (nm)	500	43	27	26-27	6,5-9,5
Composition (% total mass)					
Protein	2	10	18	25	55
Triglycerides	85	50	26	10	4
Cholesterol	4	20	34	37	17
Phospholipids	9	20	22	20	24

Lipoproteins are classified according to their density, as they can be isolated by ultracentrifugation on the basis of this criterion. This separation method then allows determination of apolipoprotein and lipid contents. The density of different lipoproteins is largely determined by their size and lipid–protein ratio. Thus, the least dense lipoproteins are the largest and have the highest lipid content. From largest to smallest, we have chylomicrons, VLDL, IDL, LDL, and HDL. Notably, different sizes and densities have been defined for different subtypes of VLDL, LDL, and HDL; therefore, each class of lipoproteins is in turn made up of different subpopulations of particles with clinical significance yet to be defined.^(12,36,51)

Chylomicrons

These are the largest and least dense lipoprotein particles ($d < 1,000$ g/ml), with a lower protein content and a large lipid component, highly enriched in triglycerides. These lipoproteins contain various apolipoproteins, including apo B-48, apo A-I, apo C-II, apo C-III, and apo E. Apo B-48 is a protein necessary for both the structure and function of chylomicrons and a specific protein marker for this type of lipoprotein.^(32,48)

The main function of chylomicrons is to supply tissues with lipids obtained from food intake, mainly triglycerides. After hydrolysis in the intestinal lumen, triglycerides are absorbed as fatty acids and re-esterified into triglycerides, packaged into chylomicrons, and then secreted into the lymph from enterocytes. They then pass from the blood to the tissues that need them most for use (muscle tissue) or storage (adipose tissue).^(44,52)

The catabolism of chylomicrons requires the action of lipoprotein lipase (LPL), an enzyme anchored in the capillaries of the aforementioned tissues that catalyzes the hydrolysis of triglycerides in chylomicrons, releasing fatty acids. LPL requires the presence of apo C-II as a cofactor to be active. This apolipoprotein is found in chylomicrons and other triglyceride-rich particles, such as VLDL, which undergo a similar lipolysis process. As a result of this process, chylomicrons are reduced in size and become known as residual chylomicrons, which are captured within minutes by hepatic receptors that recognize apo E.⁽⁵³⁾

There are different hereditary diseases that affect chylomicrons, either in isolation or in conjunction with other lipoproteins containing apo B, either due to a deficiency of LPL or its cofactor, apo C-II, or some proteins involved in the structure, intracellular processing, and packaging of chylomicrons, such as apo B, microsomal triglyceride transfer protein (MTP), and the protein homologous to SAR1 of *S. cerevisiae* (SAR1a).^(48,54)

Very low-density lipoproteins

Very low-density lipoproteins, commonly referred to by their initials, VLDLs, are also large, low-density particles ($d < 1,006$ g/ml) that are very rich in triglycerides. They also have an

apolipoprotein composition similar to that of chylomicrons, except for two essential aspects: they do not contain apo A-I, and they have the complete form of apo B (apo B-100) because the apo B editing enzyme is not expressed in the liver, where VLDL is synthesized. Apo B-100 is the structural protein of VLDL and lipoproteins that are synthesized largely from its catabolism: IDL, LDL, and Lp(a). The main stimulus for VLDL synthesis appears to be the uptake and catabolism of residual chylomicrons by the liver.^(12,51,55)

The main function of VLDL, similar to that of chylomicrons, is the transport of triglycerides and their delivery (in the form of fatty acids) to muscle and adipose tissue. The process by which fatty acids are generated from triglycerides is essentially identical to that of chylomicrons and therefore depends fundamentally on the activity of the enzyme LPL and its cofactor apo C-II. The result of this action is that VLDLs decrease, with a more even ratio of cholesterol and triglyceride content and greater density, floating in ultracentrifugation as IDLs do. Additionally, similar to what occurs in the catabolism of chylomicrons, the catabolism of VLDLs is one of the pathways for HDL synthesis.⁽⁴⁸⁾

Intermediate-density lipoproteins

Intermediate-density lipoproteins, or IDLs ($d < 1,019$ g/ml, $> 1,006$ g/ml), constitute a minority of lipoproteins that, as mentioned above, have an apolipoprotein composition similar to that of VLDLs. However, these lipoproteins are smaller and denser than VLDLs are, with a lower relative proportion of triglycerides to cholesterol, as their origin is mainly a product of VLDL lipolysis. It is believed that approximately half of IDL particles are captured in the liver by receptors that recognize apo E, whereas the other half are converted to LDL through a complex process involving hepatic lipase (HL).^(12,13,51)

The prototypical disease of IDL accumulation is familial dysbetalipoproteinaemia, which is due in part to the presence of specific genetic variants of apo E (known as the apo E2/E2 genotype) that appear to have a lower affinity for apo E-specific receptors in the liver.⁽⁴⁸⁾

Low-density lipoproteins

Low-density lipoproteins, or LDL ($d < 1,063$ g/mL, $> 1,019$ g/mL), are characterized by their apo B-100 content and have cholesterol esters as their major lipid component.⁽¹²⁾

The function of LDL is to transport and deliver cholesterol to cells, including peripheral tissues and the liver. LDLs are recognized by LDL receptors located in the plasma membrane that recognize apo B-100 and apo E. LDL receptors are synthesized by multiple cell lines and travel to the plasma membrane, where they are bound by a protein called clathrin in specific areas called coated pits. These coated pits undergo endocytosis every approximately 5 minutes, regardless of whether they have bound LDL, and are transported to the cytoplasm in the form of endosomes. If they contain LDL bound to the receptor, their protein and lipid contents are hydrolyzed to form amino acids and unesterified cholesterol. Unesterified cholesterol is toxic to cells above a certain concentration and must therefore either be used (for membrane or steroid hormone synthesis, for example) or converted by acyl-cholesterol acyltransferase (ACAT) enzymes into cholesterol esters, which can be stored as a cellular cholesterol reservoir. Once its cellular cycle is complete, the LDL receptor can be degraded by PCSK9 or recycled to start the cycle again.^(48,56,57)

Cells can also synthesize cholesterol *de novo* through a long (endogenous) synthesis pathway, which is critical for regulating the conversion of hydroxymethylglutaryl CoA (HM CoA) to mevalonate, a step catalyzed by HMG CoA reductase. However, the greater efficiency of

the LDL receptor synthesis pathway means that it predominates over the activation of the endogenous cholesterol synthesis pathway, since by synthesizing fewer proteins, they gain access to a greater number of cholesterol molecules. Intracellular nonesterified cholesterol levels coordinate the two cholesterol synthesis systems, ensuring their coordination and preventing excess intracellular cholesterol.⁽⁴⁸⁾

The proper expression and functionality of LDLRs are important determinants of the serum LDL concentration. Familial hypercholesterolemia, which is an autosomal dominant disease caused by mutations in the LDL receptor gene or, less frequently, in the apo B-100 ligand domain or PCSK9, presents with elevated serum LDL concentrations. In this context, it is important to know that the type of cholesterol-lowering drug most commonly used in clinical practice, statins, works by inhibiting HMG CoA reductase, as this increases cellular LDL receptor synthesis, which lowers serum LDL and, therefore, cholesterol concentrations.^(15,58)

High-density lipoproteins

High-density lipoproteins, or HDL ($d < 1,21 \text{ g/mL}$, $> 1,063 \text{ g/mL}$), are characterized by their apo A-I content, with cholesterol esters as their main component. On the one hand, their synthesis depends on the catabolism of triglyceride-rich particles (chylomicrons and VLDL), and on the synthesis of apo A-I, which is initially not associated with lipids, by the liver and intestine.

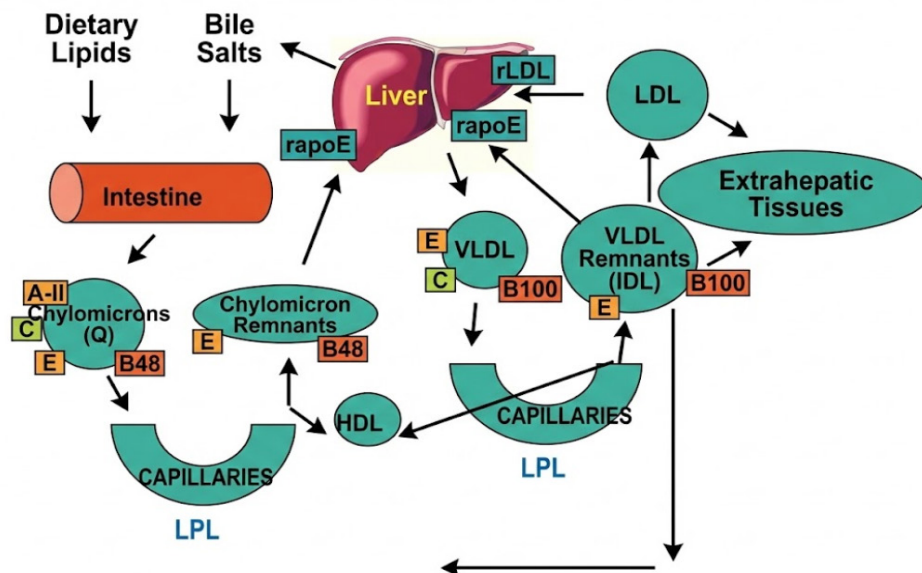
The best-known function of HDL is reverse cholesterol transport, although other functions, such as the inhibition of the oxidative modification of LDL or its anti-inflammatory and antithrombotic capacity, also appear to be highly relevant.⁽⁵⁹⁾ The function of HDL depends largely on its apo A-I content, its main apolipoprotein. This apolipoprotein facilitates the removal of excess intracellular phospholipids and cholesterol through specific mechanisms that require energy consumption. This step, known as efflux, depends on its interaction with ATP-binding cassette A1 and G1 (ABCA1 and ABCG1) transporters. To a lesser extent, there is also efflux of cholesterol from peripheral cells through the scavenger receptor B-I (SR-BI). The HDL cholesterol obtained from cellular efflux is subsequently esterified by the enzyme lecithin-cholesterol acyltransferase (LCAT), which also requires the presence of apoA-I as a cofactor. The increase in ester cholesterol in the HDL core increases the size and round shape of the HDL, until its cholesterol ester content is ultimately released to hepatocytes after they interact with SR-BI. Cholesterol captured in this way can be eliminated by bile and feces after hepatic and intestinal secretion mediated by an ABCG5/ABCG8 heterodimer. Alternatively, cholesterol can be converted in the liver into bile acids, which are eliminated via bile and feces if they are not reabsorbed in the intestine. Since cholesterol cannot be broken down by the body, reverse transport of cholesterol (and bile acids) is the only known way to eliminate cholesterol from our bodies. This explains why some cholesterol-lowering drugs, such as cation exchange resins (e.g., cholestyramine) and inhibitors of intestinal cholesterol absorption (such as ezetimibe), act at this level by inhibiting the intestinal absorption of bile acids and cholesterol, respectively.^(59,60,61)

There are different hereditary diseases caused by HDL deficiency that are caused by mutations in some of the following genes: ABCA1, APOA1, and LCAT. There are also hereditary disorders that cause increased HDL, such as those caused by mutations in the PTEC, LH, or LE genes.^(62,63,64)

Integrated metabolism of lipoproteins

Figure 1 presents an integrated view of lipoprotein metabolism, showing the very strong interrelationship between the metabolism of different lipoproteins. In this regard, several particularly noteworthy aspects exist. The first is the relationship between the efficient

catabolism of chylomicrons and VLDL and the synthesis of HDL. This fact partially explains the inverse relationship that is often found between triglyceride and HDL cholesterol concentrations in patients and populations.^(65,66,67,68) The second is that this close interrelationship between metabolism and function occurs because various metabolic and functional pathways, as discussed above, are controlled at the level of ligand activity and transcription, with some of these ligands being nonesterified fatty acids and eicosanoids.^(48,69,70,71)



Source: Errico et al.⁽⁷²⁾

Figure 1. Overview of lipoprotein metabolism

Note: Q: chylomicrons; rapoE: APOE-recognizing receptor; rLDL: LDL receptor

Triglycerides

These are acylglycerols, a type of lipid formed by a glycerol molecule whose three hydroxyl groups are esterified by three saturated and unsaturated fatty acids. Triglycerides are part of fats, especially those of animal origin. Oils are triglycerides in liquid form of plant origin or from fish. They are another type of fat found in the bloodstream and make up most of the adipose tissue in the adolescent body.⁽⁴³⁾

Triglyceride synthesis takes place in the endoplasmic reticulum of almost all cells in the body, but it occurs in the liver, particularly in parenchymal cells, hepatocytes, and adipose tissue (adipocytes), where this process is most active and of greatest metabolic relevance. Therefore, any accumulation of triglycerides in this organ is pathological and is referred to interchangeably as hepatic steatosis or fatty liver. In contrast, the main function of adipose tissue is to accumulate energy in the form of triglycerides. However, the pathological accumulation of triglycerides in adipose tissue (obesity) is apparently causally associated with a series of endocrine-metabolic abnormalities, the causes of which are currently the subject of intense research, given their impact on the overall mortality of the contemporary population. A minimal amount of triglycerides are normally stored in skeletal and cardiac muscle, but only for local consumption.^(63,64,65)

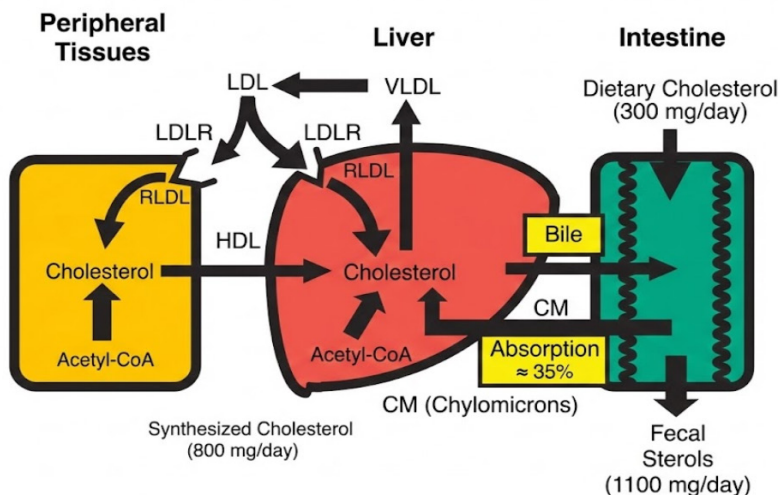
Cholesterol

Cholesterol is a component of vital importance for the structure and function of the cell membrane in vertebrates. It is essential for tissue growth and the synthesis of steroid hormones. Cholesterol metabolites, such as bile salts, steroid hormones, and oxysterols, perform important biological functions.⁽⁶⁶⁾

In mammals, cholesterol can be obtained through the absorption of dietary cholesterol (exogenous route) or de novo synthesis in the body's cells (endogenous route). The liver is the organ responsible for regulating cholesterol homeostasis. Its functions include facilitating the elimination of very low-density lipoproteins (VLDLs) and low-density lipoproteins (LDLs) and the remnants of chylomicrons containing cholesterol; synthesizing cholesterol; synthesizing and secreting high-density lipoproteins (HDLs); secreting cholesterol and bile salts into bile; and being involved in reverse cholesterol transport. Recently, however, the importance of the intestine in many aspects of cholesterol physiology has become increasingly recognized because of its significant impact on cholesterol homeostasis in terms of its reabsorption, fecal excretion, and de novo synthesis.^(12,67)

All cells in the body can synthesize cholesterol, but the liver is the central organ.⁽⁵⁰⁾ There are three ways to obtain cholesterol (figure 2):

- Cholesterol intake from the diet through chylomicron remnants.
- LDL-containing circulating cholesterol and extrahepatic tissues are taken up by rLDL, and cholesterol is taken up in the form of HDL and VLDL remnants by specific receptors.
- Synthesis of steroids from acetyl-CoA under the control of the rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase through a complex metabolic pathway (inhibited by statins).



Source: Cofan Pujol⁽⁵⁰⁾

Figure 2. Overall cholesterol homeostasis

The enzyme HMG-CoA reductase is the rate-limiting enzyme in cholesterol synthesis. Cholesterol synthesis is tightly regulated by sterol regulatory element-binding proteins (SREBPs), which are mainly type 2. When the level of cellular cholesterol is high, SREBP2 is found in

the endoplasmic reticulum, where it forms a complex with SREBP2 cleavage-activating protein (SCAP). When cells deplete sterols, SCAP accompanies SREBP2 from the endoplasmic reticulum to the Golgi apparatus, where it is cleaved to release part of the protein from the membrane. SREBP2 can enter the nucleus and bind to the sterol response element (SRE) in the promoter region of many genes involved in cholesterol synthesis, activating their transcription.^(50,66)

Atherosclerosis and serum cholesterol: endothelial disruption

The relationships among high cholesterol levels, atherosclerosis, and endothelial dysfunction have been extensively studied. Elevated serum concentrations of total cholesterol (TC), LDL-C, and VLDL-C and low serum concentrations of HDL-C correlate with the extent of these atherosclerotic lesions.⁽⁶⁰⁾ The first atherosclerotic lesions are fatty streaks, which can already appear in the aorta and coronary arteries during the first decades of life and basically consist of an accumulation of LDL-type fats in the vascular intima due to endothelial dysfunction.

Under physiological conditions, lipoproteins that penetrate the subendothelial space are returned to the circulating blood by the reverse cholesterol transport (RCT) mechanism, in which HDL participates. When endothelial dysfunction occurs, the increased permeability of the vessel wall causes an increase in LDL penetration into the vascular wall, which exceeds the speed and efficiency of the RCT system to return it to the bloodstream. In addition, some risk factors, such as diabetes and smoking, reduce the amount of HDL and further decrease the elimination of LDL.⁽¹²⁾

All these factors lead to an increase in the period during which lipoproteins remain within the subendothelial space, where they undergo mild oxidation, mainly by endothelial cells, producing minimally modified LDL (MM-LDL) molecules, which, together with the oxidative stress present in the environment, the presence of angiotensin II and reduced flow pressure, called “friction” in areas prone to atherosclerosis, are capable of activating nuclear factor kappa-B (NF-κB), a transcription factor that increases the expression of molecules involved in the steps of monocyte uptake. These molecules can be divided into two groups:⁽⁶⁸⁾

- Adhesion molecules (VCAM-1, ICAM-1, and E-selectin) are responsible for the movement and adhesion of monocytes to the blood vessel wall.
- Chemoattractant molecules (MCP-1, IL-8) cause monocytes to enter the blood vessel wall.

Once in the subendothelial space, monocytes transform into macrophages, which oxidize MM-LDL and produce oxidized LDL. This process is promoted by angiotensin II and by the prior glycosylation of LDL. Macrophages capture oxidized LDL, a process mediated by macrophage colony-stimulating factor (M-CSF) and stimulated by angiotensin II. In this way, activated macrophages can stimulate the expression of angiotensin-converting enzyme (ACE) and the synthesis of angiotensin II, leading to a positive feedback loop. Furthermore, because there is no saturation mechanism in macrophages, they continue to capture lipids and become saturated, and they continue to capture lipids and undergo overload, which causes them to degenerate, eventually becoming so-called foam cells that ultimately die and release the lipids that form the lipid core, along with toxic substances such as enzymes, free radicals, and superoxide anions. The toxic products damage the endothelium, which may even be destroyed and disappear in some areas. Macrophages and some activated platelets secrete growth factors, such as platelet-derived growth factor (PDGF), which stimulate the proliferation and migration of smooth muscle cells in the tunica media. This proliferative phase increases with decreasing levels of the antiproliferative molecule nitric oxide (NO) and with increasing levels of angiotensin II. Smooth muscle cells also secrete growth factors and, in addition, cover the atheromatous core

and produce matrix proteins (collagen, elastin, and proteoglycans), which form a fibrous cover. Once they have formed, atherosclerotic plaques can grow slowly if the atherogenic process continues, or they can suddenly become complicated.^(11,38,69)

Proper endothelial function depends on a wide variety of factors, such as the anatomical integrity of endothelial cells, correct signaling, and adequate production of vasoactive substances. Traditional risk factors such as hypercholesterolemia affect the production or action of key vasoactive substances, such as endothelial NO, which can trigger proatherogenic and prothrombotic effects.⁽⁶⁹⁾

It has been reported that mainly oxidized LDL, and to a lesser extent, nonoxidized LDL, decreases the expression of endothelial nitric oxide synthase (eNOS), which also coincides with lower eNOS activity. This promotes oxidative stress and a strongly proinflammatory state, which can lead to profound vascular alterations.⁽¹²⁾

There is evidence that the arteries of atherosclerotic animals and patients with hypercholesterolemia or atherosclerosis produce lower amounts of NO and show a reduced response to stimulus with endothelium-dependent vasodilators. This finding suggests that even before the morphological alterations typical of atherosclerosis occur, there is already a functional alteration of the endothelium as a consequence of the proinflammatory state.^(16,38,70)

High cholesterol concentrations have been shown to disrupt and alter vascular structure and function, as cholesterol adheres to the lining of the vascular wall, which consists of the endothelium, and can interfere with endothelial function, leading to lesions, plaques, occlusion, and embolism, along with reduced recovery and proper management of the lesion.^(69,71)

Poor nutrition is closely linked to the prevalence of cardiovascular disorders. The main external source of cholesterol is animal-based foods such as meat, fats, eggs, and milk. Excessive cholesterol intake causes its concentration to increase in the blood and accumulate in the body, promoting atherosclerosis. In addition to these important factors, obesity, hypertension, diabetes mellitus (DM), smoking, a sedentary lifestyle, and even socioeconomic factors increase the risk of cardiovascular problems at an early age.^(45,47,72)

On the other hand, high serum cholesterol levels are not always caused by the consumption of foods high in fat and unhealthy lifestyles. Therefore, effective treatment can be problematic when genetic conditions are present, such as familial hypercholesterolemia, which is a prime example of early-onset atherosclerosis in vivo dependent on LDL-C.^(15,58)

Hyperlipidemia, dyslipidemia, or dyslipidemia

Dyslipidemia is any alteration in plasma lipid levels (cholesterol, its fractions, or triglycerides), whether due to excess or deficiency, although it can also apply to alterations in their functions with “normal” concentrations.⁽⁷³⁾

Dyslipidemia is one of the main risk factors for ischemic heart disease, the leading cause of death worldwide. Early detection and early therapeutic intervention are key elements in the adequate prevention of CVD. Despite the wealth of evidence on its clinical management, the rate of patients who achieve good control of their lipid levels, especially patients with high and very high CVRs, is very low. The reason for this phenomenon continues to be debated, and although the problem of therapeutic compliance is prevalent in many patients, the attitudes of healthcare professionals (clinical inertia) are a problem that contributes to the inadequate

control of CVR factors.^(74,75)

These pathological conditions, whose only common element is an alteration in lipid metabolism with a consequent alteration in the concentrations of lipids and lipoproteins in the blood, translate in laboratory tests into an increase in circulating cholesterol, triglycerides, or both.⁽³⁴⁾

Notably, the concentration of plasma lipids in the blood follows a continuous or normal distribution, with large variations depending on factors such as age and sex, making it very difficult to determine which blood lipid concentration values are pathological.⁽⁷⁵⁾

Factors that contribute to the onset of hyperlipidemia include genetic factors, with polygenic transmission being the most important; environmental factors, such as a diet rich in saturated fats; alcohol, which can cause a significant increase in blood triglyceride levels; excess weight; and a lack of physical exercise.^(16,76,77)

Dyslipidemia can be classified as follows:⁽³⁴⁾

- Primary: those not associated with other diseases. Generally, genetic origin and familial transmission (hereditary) are the least frequently determined forms, such as familial hypercholesterolemia, where the increase in lipoproteins is due to alterations in the synthesis and metabolism of various components, both lipids and proteins.
- Second, the basis of the alteration is associated with an adjacent disease.

The most common and important dyslipidemia due to its etiopathogenic significance in cardiovascular diseases is hypercholesterolemia, which is defined as the presence of excessively high levels of cholesterol in the blood.⁽³⁷⁾

The diagnosis is based on the detection, on an empty stomach, of elevated triglyceride and/or cholesterol levels above the 95th percentile for the patient's age and sex. Lipoprotein electrophoresis on agarose gels helps determine the type of lipoproteins affected.⁽⁷⁵⁾

From a practical point of view, hyperlipoproteinaemia can be grouped into the following categories:^(57,78)

- a. Hypercholesterolemia alone: this is usually due to increased LDL levels (type IIa hyperlipoproteinemia), although it is rarely associated with increased HDL (hyperalphalipoproteinemia).
- b. Combination of hypercholesterolemia and hypertriglyceridemia: this is often due to elevated VLDL and LDL (type IIb hyperlipoproteinemia).
- c. Increased triglycerides: if moderate, it is usually due to increased VLDL (type IV), and if severe, to increased chylomicrons (type I), increased VLDL (type V), or increased beta-VLDL (type III).

The same lipoprotein phenotype may be due to several genetic alterations, but in clinical practice, measurements of cholesterol, triglycerides, HDL cholesterol, and plasma lipoprotein electrophoresis are sufficient to establish a diagnosis and initiate treatment.⁽⁷⁹⁾

Sometimes, the diagnosis is made in the absence of symptoms and signs, on the basis solely of a family history of hyperproteinaemia or young patients with ischemic heart disease or early death from cardiovascular disease.⁽⁴⁰⁾

The NHLBI recommends the following guidelines for cholesterol levels in children and adolescents (aged 2-19 years) from families with high blood cholesterol levels or early heart disease:⁽³⁴⁾

Table 2. Pediatric Cholesterol Guidelines		
	Total cholesterol	LDL cholesterol
Acceptable	Less than 170 mg	Less than 110 mg
Borderline	between 170 and 199 mg	between 110 and 129 mg
High	200 mg or more	130 mg or more

The atherosclerotic process begins in childhood and progresses slowly during adolescence, subsequently leading to the development of ischemic heart disease. Risk factors that accelerate atherosclerosis and ischemic heart disease in adults, including hypercholesterolemia, also act at a young age.⁽³⁸⁾

Lipid concentrations in childhood are predictors of those that will occur in adulthood.⁽⁴⁰⁾ Some authors have highlighted the relationship between the presence of severe atherosclerotic lesions in adolescents and lipid concentrations prior to their death.⁽⁸⁰⁾

In this context, the presence of familial hyperlipidemia increases the risk of developing premature ischemic heart disease. It is recommended that TC be determined in children with a family history of premature cardiovascular disease or when one parent has familial hyperlipidemia.^(81,82)

In patients with FH, lifestyle modifications should be implemented to reduce LDL-C and risk factors for cerebrovascular disease, even though the degree of LDL-C reduction is modest and variable, being approximately 10 %. A diet containing less than 7 % saturated fat and less than 200 mg of cholesterol should be recommended. Although there are different points of view, there is a consensus that fresh fruits and vegetables should be consumed, as they are rich in nutrients such as vitamins and minerals and are abundant in dietary fiber, which comprises carbohydrates that are not absorbed and therefore provide few calories.^(45,49)

Patients should be encouraged to achieve a healthy weight through physical activity and adequate caloric intake. Alcohol consumption and smoking should be restricted, as they are associated with cardiovascular disease in patients with hypercholesterolemia.^(40,83,84)

Dietary treatment is essentially based on three fundamental premises:^(49,85)

- a) Reduce cholesterol intake to < 300 mg/day, except in cases of pure hypertriglyceridemia; to do this, it is good to remember that one egg has 250 mg of cholesterol and that one cup of regular milk has 32 mg.
- b) Total fat intake should be reduced so that it does not exceed 30 % of total daily calories.
- c) Increasing the ratio of unsaturated to saturated fatty acids above 1, as a predominance of saturated fatty acids increases the cholesterol concentration.

A more restrictive diet is impractical because food loses its appeal and, in the long run, people fail. Only in special cases should fat intake be reduced further: 200 mg/day of cholesterol and 25 % of total calories from fat, of which only 8 % should be saturated.^(86,87)

In recent years, the extraordinary usefulness of reducing cholesterol levels has become apparent, especially in preventing the progression (but also in achieving regression) of atherosclerotic lesions in patients with CHD.^(58,68)

There are a wide variety of drugs useful in the treatment of hyperlipidemia, including ion exchange resins such as colestipol, nicotinic acid, fibrates, probucol, and statins, which are the most recent drugs to appear, such as lovastatin.^(37,88,89)

Various studies have shown a relationship between cardiovascular risk factors in children and those present in their parents and relatives.^(32,90,91,92)

The genetic basis of hypertension is accepted by most authors in relation to its aggregation and familial recurrence. Under this condition, i.e., hypertension, the association between genetics and the environment can be most clearly observed. Hypertension can be considered the most prevalent disease among polygenic disorders in Western countries.^(15,93,94)

Some authors have reported a relationship between the angiotensinogen gene and HTN.^(95,96,97)

Other authors report an association between plasma lipid concentrations among siblings, with differences observed according to the sex of the pairs. The association was positive for male pairs and less so for mixed pairs and negative for female pairs. All of the above findings suggest genetic inheritance linked to the sex of these lipid factors. There was also a weaker association with body mass index values. Finally, the aggregation of BP values between siblings in this study is quite weak.^(98,98,99)

Knowledge of risk factors for CVD in children is a very useful strategy, as it allows preventive measures to be established at an early age. There is favorable scientific evidence showing that the application of preventive strategies in various populations, in which education or knowledge about risk factors and the implementation of related preventive measures have led to a decrease in the incidence of cardiovascular disease, whereas in those where these actions have not been implemented, the development of this type of disease continues to rise.^(76,100) Therefore, early screening of overweight children should be the first step in assessing their nutritional status. By offering optimal healthcare and education, the risk of developing cardiovascular complications can be significantly reduced. It is important to help people with hyperlipidemia obtain knowledge, especially about diet, and the skills necessary to manage their disease so that they can lead a full and healthy life because prevention is better than curing, and promoting health is better than preventing disease.^(77,101)