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Classification of Primary and Secondary Dyslipidemias Revisited

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ABSTRACT

The present revision brings the main characteristics of the different manifestations of hyperlipidemias. In each form there is one or more lipoprotein alterations, manifesting risk when apoprotein B lipoproteins are increased or when apoprotein A lipoproteins are decreased. The interest in this issue has to do with the cardiovascular risk that it involves. Normal or "goal" values vary from patient to patient depending on their clinical features, family history and lipid profile itself. Not only are there genetic heritage involved in the serum levels of cholesterol of each lipoprotein but also secondary causes have to be considered such as hypothyroidism for example as well as the use of some medications metabolized in the liver. The presence of xanthomas strongly corroborates being primary or genetic the cause of the dyslipidemia. The collection of samples can be made in a non fasting condition for two measurements only: total cholesterol and HDL cholesterol. In the impossibility of not being able to draw a fasting sample, risk evaluation can be evaluated by the non HDL cholesterol value. Recently a new formula for calculation of LDL cholesterol independent of triglycerides concentration is being used, Martin's formula. Quality control of the techniques involved in the assays must always be checked by the laboratories and the updated reference values should always accompany the results sheet.

Abbreviations

HDL-c: High Density Lipoprotein Cholesterol; **IDL**-c: Intermediate Density Lipoprotein Cholesterol; **LDL**-c: Low Density Lipoprotein Cholesterol; **Lp(a):** Lipoprotein (a); **Non HDL-c:** Non HDL-cholesterol; **VLDL**-c: Very Low Density Lipoprotein Cholesterol.

In general, patients who come to our care for lipid assessment bring with them laboratory tests. It is a basic mistake to check the results of these tests before a normal consultation. As with any clinical evaluation, anamnesis and physical examination data should be considered prior to laboratory evaluation.

The clinical approach of dyslipidemic patients aims to:

- decrease the occurrence or recurrence of cardiovascular pathology, i.e., coronary, cerebral and peripheral heart failure;
- prevent, diagnose and treat episodes of acute pancreatitis caused by severe hypertriglyceridemia, which correspond to 15% of cases;
- diagnose and treat skin changes due to hyperlipidemias.

Anamnesis

The collection of accurate information on the anamnesis, from identification to family history, provides support for the etiological diagnosis of dyslipidemia, as well as for the stratification of cardiovascular risk due to the coexistence of risk factors in the same patient.

Therefore, age, sex, origin, the characterization of eating habits and lifestyle, the time of diagnosis of dyslipidemia, the reference

to symptoms related to anatomical and functional alterations promoted by hyperlipidemia in target organs, the use of drugs, the presence of pathologies, which promote secondarily the elevation of lipemia, or even the occurrence of dyslipidemias in several elements of the same family are extremely important in the patient's approach.

Physical examination
Changes in physical examination specific to dyslipidemias depend on lipid depot in different regions of the body. It occurs in a small number of patients, who may present such deposits in the skin, eyes and viscera.

Xanthomas are skin lesions resulting from lipid deposition in the skin. Lipoproteins (VLDL-c, IDL-c and LDL-c - Very Low, Intermediate and Low Density Lipoproteins), at high levels in the circulation, reach the subendothelial space, where they are internalized by macrophages, which accumulate in areas of great tension or friction, such as tendon sheaths, skinfolds, elbows, knees, back of hands, promoting the formation of xanthomas. Xanthomas do not always correspond to the clinical expression of dyslipidemias, and may also form normolipemic due to local dermal changes.

They can be classified based on their appearance or location. So, we have:
- Flat xanthomas: they are slightly elevated flat yellowish plates, which can be located in different regions of the body. When located in eyelids or periorbital region, they are called xanthenaemas, while when found in the palms along the crests of the palm and fingers regions, they are designated palm xanthomas. They can be seen in type II and III hyperlipidemias.
- Tuberous xanthomas: are isolated or grouped nodules of yellow color, of different sizes, located on elbows, knees, thighs and buttocks. May occur in type IIa and III hyperlipidemias.
- Tendinous xanthomas: they are yellow nodules, which form along fascial and periosteum tendons. They are preferably located on the back of the hands and feet and in the Achilles tendon. They are sometimes diagnosed on palpation, as a certain thickening in tendons. They are found in type II hyperlipidemias.
- Eruptive xanthomas: they are yellowish papulous lesions encased by an erythesinhalous halo, occurring in the buttocks and back or any other part of the body. The important increase in triglycerides is related, being observed in type I, IV and V hyperlipidemias.

The ocular alterations that can be found in dyslipidemic patients are the corneal arch and retinal hyperlipemia.

The corneal arch is a white halo that occurs around the iris, being associated with cholesterol and triglyceride elevations. Differential diagnosis should be made with the senile arch, which can occur in individuals over 50 years of age and with the Kayser-Fleisher ring of brown and pathognosome color of Wilson's disease. Retinal hyperlipemia is a modification of retinal color ation and its vessels evaluated on the fundus examination, which become opalescent or milky due to infiltration of fatty material, particularly triglycerides. It is found in type I and V hyperlipemias.

Visceral involvement occurs by infiltration of lipids into viscera such as liver and spleen. Hypertrophy of these organs can be observed in severe hypertriglyceridemias.

Laboratory tests
Since the diagnosis and treatment of dyslipidemias are based on laboratory tests, it is essential that criteria be adopted regarding the sample collection and methodology used to perform these analyses [1].

Sample collection
For a blood sample to be adequate for analysis it is important to observe a fast of 12 to 14 hours. Otherwise, there is a risk of obtaining triglyceride values falsely increased by the presence of chylomicrons of food origin and their remnants.

On the day before collection, the patient should maintain his usual diet, avoiding food abuse or ingestion of excessive amounts of alcohol, which could also elevate triglyceridemia.

Physical activity should not be modified prior to blood collection. Physical exercise before collection can reduce triglycerides by the general increase in metabolic activity for energy purposes.

Venous puncture should be performed after the patient has remained seated or lying down for about 5 minutes. Postural variations can modify the results. Prolonged venous statism (more than 2 minutes of tourniquet use) should be avoided as it may promote hemoconcentration and lead to an increase in all elements of the lipid profile.

Collection up to three weeks after a mild illness or up to three months after serious illnesses should be avoided, as cholesterol levels are reduced and triglyceride levels increased in these situations. Exception can be made in the case of acute myocardial infarction, when it is desired to start early treatment of dyslipidemias in the secondary prevention of atherosclerotic disease.

Finally, the patient should be asked about the use of medications that may alter the lipid profile, a common cause of secondary dyslipidemia.

The results obtained in the determination of serum lipids are subject to biological, pre-analytical and analytical variations, which can be quantified by their respective coefficients of variation.

Analytical modifications depend on the laboratory method employed, which should be as accurate and accurate as possible. The higher the accuracy (indicates how much the value found approaches the actual value) and the accuracy (expresses the reproducibility of the results in multiple dosages), the lower the coefficient of analytical variation and consequently the more reliable the examination.

It is allowed for total cholesterol an acceptable maximum variation of 5%, for High Density Lipoprotein Cholesterol (HDL-c) of 10% and for triglycerides of 20%, in repeated dosages. Ideally, total cholesterol variations should not exceed 3% [1].

The following methodologies can be used to determine serum lipids:

Ultracentrifugation: allows the separation of lipoproteins based on their different densities. The higher the lipid content, the lower the density. Thus, when the blood sample is subjected to a centrifugal force, in a known density medium, the particles less dense than the medium float, while the denser ones are deposited at the bottom of the tube. It allows the separation of all lipoproteins - chylomicrons, VLDL (very low density lipoprotein), IDL-c (intermediate density lipoprotein), LDL-c (low density lipoprotein), HDL-c (high density lipoprotein) and Lp(a) (Lipoprotein a). It is not suitable for daily laboratory routine, as it is a method that requires expensive technical resources.

Lipoprotein electrophoresis: a method that is based on the property of proteins becoming negatively charged when placed in a medium with pH higher than its isoelectric point, within an electric field. Thus, when a serum sample is placed in a support medium (agarose, cellulose gel, polyacrylamide), the apoprotein component of lipoprotein, negatively charged, causes them to migrate to the positive pole of this electric field. With migration, lipoproteins are broken into bands, depending on their size and the number of negative charges that the apoprotein component contains. In clinical practice, lipoprotein electrophoresis is important in the laboratory diagnosis of type III dyslipidemia, because it identifies and quantifies the IDL-c fraction.

Colorimetric enzymatic method: it is the most commonly used method currently for cholesterol and triglyceride dosage. The HDL-c fraction is also determined by colorimetric enzymatic method after being separated by precipitation of other lipoproteins. It has good accuracy and accuracy, has low cost and allows automation.

The vast majority of dyslipidemic patients can be followed by the lipid profile, which is constituted in the determination of total cholesterol, triglycerides and HDL-c by this method, and the calculation of the LDL-c fraction by Friedewald's formula, i.e.:
LDL-c = Total Cholesterol - (Triglycerides/5* + HDL-c)
*(Triglycerides /5 = VLDL-c)

Friedewald's formula can be used in LDL-c determination when triglyceride values do not exceed 400 mg/d when there are no chylomicrons in serum and in the absence of type III dyslipidemia [2]. In these situations, it is recommended to use another method for the determination of serum lipoproteins.

In cases of augmented triglycerides Martin Hopkins new formula can be used [3].

$$LDL\text{-}c = \frac{TC}{0.948} - \frac{HDL\text{-}c}{0.971} - \left(\frac{TG}{8.56} + \frac{TG \times Non\text{-}HDL\text{-}c}{2140} - \frac{TG^2}{16100} \right) - 9.44$$

Evaluation of results: The results should be confirmed by the repetition of the tests performed one to two weeks after the first collection. If the values of the second determination differ in more than 5% from the first for total cholesterol dosage, in more than 10% for HDL-c and in more than 20% for triglycerides, a third dosage should be performed after one to two weeks, considering as a real value the one represented by the mean of the two closest values [1].

Diagnosis of dyslipidemias

Lipid profile determination: Prospective epidemiological studies conducted in recent decades have shown that there is an exponential relationship between serum cholesterol level and coronary atherosclerotic disease, justifying the adoption of measures that allow the early diagnosis of dyslipidemias.

Therefore, men and women from 20 years of age should have their lipid profile determined. In relation to children and adolescents (age between 2 and 19 years), the determination of serum lipids should be performed in those who have clinical manifestations of dyslipidemias, risk factors for atherosclerotic disease, family history of dyslipidemia or premature atherosclerotic disease in first-degree relatives (before 55 years in men and 65 years in women). Obviously, regardless of age group and gender, the determination of lipid profile should be performed in individuals with established atherosclerotic disease.

Reference values: As long as reliable values of the different lipid variables are obtained; we must compare them with the reference values for characterization of dyslipidemia. The reference values of serum lipids, accepted internationally for children and adolescents and for adults (individuals aged 20 years or older), are found in Tables 1, 2 3 and 4 [1].

Table 1: Reference values for lipids and lipoproteins in children and adolescents [1].

Lipids	Fasting (mg/dL)	No fasting (mg/dL)
Total cholesterol	< 170	< 170
HDL-cholesterol	> 45	> 45
Triglycerides (0-9 years) (10-19 years)	< 75 < 90	< 85 < 100
LDL-c	< 110	< 110
Non-HDL-cholesterol	< 145	< 145

LDL-c: low-density lipoprotein cholesterol.

Table 2: Reference values, according to estimated cardiovascular risk assessment, for adults over 20 years of age [1].

Lipids	With fasting (mg/dL)	No fasting (mg/dL)	Risk category
Total cholesterol	< 190	< 190	Desirable
HDL-c	> 40	> 40	Desirable
Triglycerides	< 150	< 175	Desirable
	< 130	< 130	Low
	< 100	< 100	Intermediate
LDL-c*	< 70	< 70	High
	< 50	< 50	Too high
	< 160	< 160	Low
Non-HDL-c	< 130	< 130	Intermediate
	< 100	< 100	High
	< 80	< 80	Too high

LDL-c: low-density lipoprotein cholesterol; Non-HDL-c: non HDL cholesterol.
*Values for LDL-c calculated by Martin's formula.

Lp(a) levels are considered as risk indicators when higher than 25 mg/dL, and fibrinogen when higher than 300 mg/dL based on epidemiological studies.

Triglyceride levels should be evaluated in conjunction with LDL-c and HDL-c levels. In the presence of low HDL-c levels the desirable triglyceridemia values are those less than 150 mg/dL.

Table 3: Percentage reduction and absolute therapeutic goals of LDL-c and non-HDL cholesterol for patients without or using lipid-lowering [1].

Risk	No lipid-lowering	With lipid-lowering	
	Reduction (%)	LDL-c goal (mg/dL)	Goal of non HDL-c (mg/dL)
Too high	> 50	< 50	< 80
High	> 50	< 70	< 100
Intermediate	30-50	< 100	< 130
Low	> 30	< 130	< 160

LDL-c: low-density lipoprotein cholesterol; Non-HDL-c: non-HDL cholesterol.

Table 4: LDL-c targets in children and adolescents, according to cardiovascular risk profile [1].

LDL-c Levels	Risk
< 190 mg/dL	No other risk factor
< 160 mg/dL	Early coronary insufficiency in the family OR another risk factor
< 130 mg/dL	Established coronary insufficiency OR 2 diseases or high-risk factors OR 1 disease or high-risk factor or 2 diseases or moderate risk factors

LDL-c: low-density lipoprotein cholesterol.

Classification of dyslipidemias: Dyslipidemias can be considered primary when related to genetic and environmental changes, or secondary when associated with a number of conditions and diseases, or the use of medications (high-dose thiazoid diuretics and prolonged use, beta-blockers without intrinsic simpathomimetic activity, corticosteroids, cyclosporine, progetogenous, retinoid) [4]. Through anamnesis, physical examination and specific laboratory tests, secondary dyslipidemias can be diagnosed. The main causes that condition secondary changes in lipid profile are found in Chart 1.

Chart 1: Causes of secondary dyslipidemia.
Diabetes mellitus
Hypothyroidism
Nephrotic syndrome
Chronic renal failure
Drugs
Obesity
Alcoholism
Pregnancy
Gout
Parenchyma liver disease
Chronic calculus collecistopathy
Multiple myeloma
Systemic lupus erythesus
Glycogen stock disease
Lipodystrophy
Osteogenesis imperfecta
Tangier's disease
Stress

In the characterization of the type of dyslipidemia found, in a practical way we can rely on the results of laboratory tests performed [1]. So, we can find:
- Isolated hypercholesterolemia - isolated increase in serum cholesterol;
- Isolated hypertriglyceridemia - isolated increase of the serum triglycerides.
- Mixed hyperlipidemia - increased cholesterol and serum triglycerides.
- Hypoalphalipoproteinemia - reduction of HDL-c fraction alone or associated with changes in LDL-c and/or triglycerides.
- Hyperalphalipoproteinemia - increased HDL-c fraction alone or associated with LDL-c changes.

We can also use Fredrickson's phenotypic classification to characterize primary dyslipidemias. This classification, which is based on electrophoretic separation of lipoprotein fractions, does not take into account HDL-c levels, apoproteins and genetic alterations. The main characteristics of dyslipidemias, according to this classification, are found in Chart 2 [5].

Advances in cell and molecular biology have made it possible to classify dyslipidemias also on a genetic basis. So we have:
- Polygenic hypercholesterolemia - promotes increased total cholesterol and LDL-c. It is the most frequent cause of hypercholesterolemia, affecting about 85% of individuals with phenotype IIa. The transmission pattern is polygenic, reflecting the interaction of multiple factors (genetic and environmental).
- Family hypercholesterolemia - also promotes increased total cholesterol and LDL-c. It is transmitted by autosomal dominant inheritance, being found in homozygous (1:1.000.000 people) or heterozygous (1:500 people). In the homozygous form, the individual does not present receptors for LDL-c uptake, while in the heterozygous form, these receptors are reduced.
- Family hypertriglyceridemia - increased triglycerides observed

Chart 2: Phenotypic classification of hyperlipidemias.

Phenotype	Lipoproteins (main change)				Plasma Lipids (most common values)		Appearance of plasma or serum
	Chylo	VLDL-c	IDL-c	LDL-c	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	
I	↑↑↑				160 - 400	1500 - 5000	creamy sobrenatant
IIa				↑			
				a	> 240	> 200	transparent
				↑↑↑			
IIb		↑		↑			
		a		a	240 - 500	200 - 500	cloudy
		↑↑		↑↑↑			
III			↑↑				
			a		300 - 600	300 - 600	cloudy
			↑↑↑				
IV		↑					
		a			< 240	300 - 1000	cloudy
		↑↑↑					
V	↑	↑					
	a	a			160 - 400	1500 - 5000	creamy top layer
	↑↑↑	↑↑↑					blurred bottom

*The intensity of the increase of the various lipidic variables is represented by arrows.

Chylo: Chylomicrons, VLDL: Very low density lipoprotein, IDL-c: Intermediate density lipoprotein, LDL-c: Low density lipoprotein.

may be associated with hyperglycemia and hyperuricemia. It is transmitted by autosomal dominant inheritance, being found in 1:300 or 1:400 individuals. There is an increase in hepatic production of VLDL-c.

- Family hyperquilomicronemia - leads to increased triglycerides at the expense of the important rise of chylomicrons. It is transmitted by autosomal recessive gene, affecting 1:1.000.000 individuals. It occurs due to deficiency in the formation of lipoprotein lipase or its cofactor, apoprotein C-II.
- Combined family hyperlipidemia - there is an alternation of the lipid profile presented by the patient over time, or with high levels of one lipoprotein, or other, or even combined patterns. Other individuals in the family have the same characteristics. Occurs in 1:300 individuals. It is transmitted by autosomal dominant inheritance, promoting increased production of lipoproteins that contain apoprotein B-100.
- Family dysbetalipoproteinemia - there is an increase in cholesterol and triglycerides at the expense of IDL-c. It affects from 1:100 to 1:300 individuals, being secondary to structural alterations of apoprotein E, impairing the interaction with the hepatic B-E receptor.

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