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The art of interpretation (About dyslipidemias)

El arte de la interpretación (Sobre las dislipidemias)

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Science can be described as art of systematic oversimplification.
Karl Popper

Dyslipidemias have a very close relationship with the broad nosological spectrum of atherosclerosis. The correct diagnosis of lipid disorders, immersed in the genetic, epigenetic, organic, and behavioral contexts of each patient, is essential to establish the most appropriate therapeutic approach. The above concept is easily expressed in just a few words, but the exercise is much more complex than it seems, because it requires the employment of hermeneutical tools and a rather complicated integrative process of knowledge and experience. After all, despite multiple attempts to use computational techniques, till the date, machine computers have not been able to outperform the ability of human brain in carrying out these tasks.

It is a common place to say that medicine is a science as well as an art. Indeed, is an applied science (the application of scientific knowledge to solve specific practical problems), but at the same time, it is an art, because its practice demands skills that practitioners have to get through learning experience, observation, or clinical research.[1] In that way the practicing physician, based on the scientific platform of lipidology, puts into practice the art of diagnosing and treating lipid disorders.

It is undoubtedly correct to refer to the lipid profile (the measure of the serum concentration of main lipids and lipoproteins) as something individual and unique for each considered patient. The science and art of medicine must unveil the lipid abnormalities through the interpretation of this profile into a more extensive clinical setting. The word *interpret*, derived from the Latin *interpretari*, has multiple and practical connotations, from which the term is defined as the meaning or explanation of something, to the elucidation of events or acts that can be understood in different ways. Interpretation reveals the meaning of some reality. For example, the art and technique of interpret texts (hermeneutics) leads to the discovery of their true meaning. In other words, interpretation gives meaning to expressions, texts, signs, numbers, or ideas. However, for Edgar Morin reality perceptions «are both translations and brain reconstructions». This fact implies that representation and interpretation of observational facts are subject to the risk of error and illusion.[2]

Scientists often generate working models that conceptually represent systems, ideas, hypothesis, or real physical, natural or biological phenomena. These scientific models must be confronted with our current knowledge, and they also must be verified by observations or research. Lipid metabolism is so complex that challenges the ordinary modelling processes used by scientists.[3] However, one of the most important duties of scientific medicine is to clarify to the practitioner those metabolic and physiological complexities, to provide pragmatic and useful tools that allow them to carry out their daily clinical tasks.

Some applicable concepts that we use in the interpretation of phenomena or data, are the following. *«Normal»*, means a usual, current, or accepted characteristic or value,

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without exceeding or being below the average. «*Optimal*», in the other hand, signifies what is the best or insuperable, while «*desirable*», denotes a convenient acceptance to what is fair and correct for a given circumstance. On its part, «*high*», designates something above the considered usual or averaged values or concepts. «*Index*», means sometimes a quotient relating two variables (body mass index, waist-hip circumferences, etc.). In times, the term is applied to a variable normalized to compare values in different individuals: cardiac index, indexed ventricular volumes, etc. Very often, an index is a non-dimensional or pure number, without defining physical units (as Woods peripheral resistance units). In mathematics, an index is a number which is raised to a power. This one is also an index, signifying how many times it is necessary to multiply the number by itself. Finally, ratio is a proportion, the relation between two amounts. Such concepts are used very frequently to qualify clinically many variables as blood pressure, body temperature or serum lipids and lipoproteins concentrations, among many others.

Table 1 shows the interpretation of serum lipids and lipoproteins values, according with the experts of the Third Adult Panel of Treatment (ATP III), part of the National Cholesterol Education Program (NCEP), published in 2001.[4] The accepted «normal» values of lipids and lipoproteins have evolved drastically, from the time when the impact of lipids on cardiovascular events was practically unknown or underestimated, to the present day where scientific evidence has solidly established the role of lipids in atherogenesis. In recent times, the concept of «desirable values» is linked to the cardiovascular risk of each patient, according to the number and severity of the accumulated risk factors, the age, gender and already presence of cardiovascular disease. At higher risk, the decrease in atherogenic lipids should be greater. Contrary to what happens with the concentration of blood glucose or the level of blood systemic pressure, with serum lipids concentrations seem that there is not the so-called J-curve, that is, a rise in pathogenicity when very low levels of these variables are reached. *Table 2* shows the new target goals proposed by the European Society of Cardiology and the European Atherosclerosis Society (EAS).[5] Those values of LDL are not in fact «very low» concentration of atherogenic lipids and lipoproteins, bur instead represent their true physiological levels found in anthropomorphous apes, contemporary hunters-gatherers tribesmen, vegetarians, and human babies.

Table 3 shows the different composition of lipoproteins, that explains its physiologic and pathogenic behaviors. A differential characteristic of lipoproteins is the type of apolipoprotein that are structural part of their phospholipid/cholesterol cover. Apo B and Apo E, for example, function as ligands of high-affinity receptors in the liver and other tissues, which remove atherogenic lipoproteins from the circulation, while C-II apolipoprotein acts as a coenzyme of the capillary lipoprotein lipase which hydrolyze the triglyceride load of CHY and VLDL, and A-I apolipoprotein performs many activities, as reverse cholesterol trafficking, as well as numerous immunologic, anti-inflammatory, and anticoagulation actions.[6-8]

Table 1: Lipids and lipoprotein values, according with the ATP III.[4]

Lipid or lipoprotein, mg/dL	Interpretation
Total cholesterol	
< 200	Desirable
200-239	Borderline high
≥ 240	High
LDL cholesterol	
< 100	Optimal
100-129	Near optimal
130-159	Borderline high
150-189	High
≥ 190	Very high
HDL cholesterol	
< 40	Low
≥ 60	High
Triglycerides	
< 150	Normal
150-199	Borderline high
200-499	High
≥ 500	Very high

Table 2: New goals for LDL-c according with the risk category.

Risk category	LDL-c therapeutic goal, mg/dL
Low risk	< 115
Moderate risk	< 100
High risk	< 70
Very high risk	< 55

Although the paradigm of LDL-c «the cholesterol hypothesis» remains one of the strongest pillars of primary and secondary prevention of atherosclerosis, technological innovations, and current clinical and basic research, however, have expanded the relation between lipid pathology and atherosclerotic cardiovascular diseases (ASCVD). The role of hypertriglyceridemia in this regard has been somewhat underestimated, especially by the United States lipid guidelines. Notwithstanding, there is growing and compelling evidence about the importance of triglycerides (TG) and triglyceride-rich lipoproteins (TRLs) in the development of atherosclerosis and its cardiovascular outcomes, including death, mainly in overweighed/obese, insulin-resistant, aged patients. So, the cholesterol contained in very-low-density and intermediate density lipoproteins, are more atherogenic than LDL-c in this type of patients. This recognition is even more pertinent in our country, where hypertriglyceridemia and atherogenic dyslipidemia, linked to abdominal obesity and insulin resistance, affect a considerable proportion of our population.[9]

The importance of Lp(a), a small variant of LDL, with single copies of Apo B100 and apolipoprotein a has been extensively studied. It seems that is involved in several activities, as angiogenesis, tumor growth, inflammation, thrombosis, and atherogenesis, among others. Probably the cut-off value of Lp(a) is about 500 mg/L, from which the cardiovascular risk rises, although it has not been established in all ethnic groups.[10,11]

Interpretation of the lipid profile in clinical grounds is aimed to two main purposes: the estimation of the risk of suffer an episode of ASCVD or acute pancreatitis. *Table 3* concentrate different variables and markers of lipid atherogenicity. Instead, only TRLs, TG themselves, and the ratio TG/HDL-c, are markers or predictors of pancreatitis risk. Probably, in a not-too-distant future, we are going to change drastically the manner of interpret lipid and lipoprotein profile. The quantification of the number and size of atherogenic lipid particles, mainly the small and dense LDL will be the correct form of express lipid pathology.[12] But by the time being, as the most accurate method of measure LDL-c is by means of a costly and time-consuming ultracentrifugation technique, in practice generally is estimated employing the Friedewald's[13] formula:

$$LDL\text{-}c = TC - HDL\text{-}c - (TG/5)$$

The quotient TG/5 comes from the fact that in VLDL particles, cholesterol represents 20% of the lipid mass. The accuracy of the formula starts to decrease with a TG value of 250 mg/dL.[14] If TG exceed the value of 400 mg/dL, the formula is not applicable at all.[14] Despite how cheap and easy it is to estimate LDL-C in such manner, the method is very coarse and subject to many sources of error. To make the question more troublesome, if the European recommendation of measure non-fasting TG is followed, in many more patients, Friedewald formula will be less useful. US Guidelines[15] recommends the Martin adjustable reformulation of Friedewald equation for the estimation of LDL-c:

$$LDL\text{-}c = TC - HDL\text{-}c - (TG/\text{adjustable factor})$$

The adjustable factor can be selected from a table formed by the relation between TG and non-HDL-c values *(Table 4)* obtained from data of almost a million cases in which LDL-c was measured by ultracentrifugation. But again, the adjusted formula cannot be used in severe hypertriglyceridemia. The Sampson[16] formula, a rather complicated mathematical approach, seems to be more accurate and useful in the presence of severe hypertriglyceridemia, but still

needs more clinical verification. Other techniques for the estimation of LDL-c are the direct homogenous assays (not requiring ultracentrifugation), whose technical description is beyond the limits of this article. Suffice to say that these techniques have not attained universal acceptance for accuracy, complexity, and cost considerations.[14] Finally, as previously stated, a very promising method is the quantification of LDL particles, and the estimation of their size, by nuclear magnetic resonance (NMR) spectrometry. With this advanced and innovative technology, the atherogenic profile of patients can be easily disclosed.[12] The method not only measure directly and rapidly lipids and lipoproteins, but also the number of LDL particles and its subclasses, providing similar information about VLDL and HDL. *Table 4* exhibits the optimal or desirable values of all the lipid and lipoprotein variables commonly used to profile the ASCVD risk.

It is difficult to understand that to date in the first-contact clinics of our national health system, the complete profile of basic lipids is not measured, but only TC and TG. It is impossible, as was already discussed above, with these meager data, to correctly estimate the risk profile of the patient and establish accordingly the appropriate treatment or the decision to send the patient to a higher level of care. If this is done for financial and savings reasons, in the long run the cost of ASCVD care colossally exceeds the relatively cheap price of a good preventive medicine.

A special consideration about the laboratories reports is necessary. In general, with a few exceptions, the way in which public and private laboratories report lipid and lipoproteins results is outdated, causing confusion, anxiety, and discontent in both patients and practitioners. The inadequate use of «normal or reference values» may cause uncertainty in physicians and patients, and lead to erroneous, sometimes catastrophic, decisions. We must propose strongly that all laboratory reports do not include those misleading and confusing terms *«reference or normal values»*. Instead, it would be helpful the following legend: *The interpretation of the reported values is the responsibility to the treating physician. This interpretation will be carried out in accordance with the individual cardiovascular risk level.*

In conclusion, the art and science of interpreting lipid data must be a generalized instrument in the hands of every physician. The correct diagnosis and treatment of dyslipidemias are one of the strongest pillars where cardiovascular prevention is supported.

Table 3: Composition of lipoproteins.

Lipoprotein	Cholesterol (%)	Triglycerides (%)	Apolipoprotein(s)	Density, g/L	Size, nm
Chylomicrons	5	90	A-I, A-II, A-IV, B48, C II, E	< 0.95	50-500
Remnants of chylomicrons	Triglyceride content > cholesterol		B48, E	< 1.006	< 30
	Variable relationship				
Very low-density lipoprotein	20	65	B100, C II, E	< 1.006	30-80
Intermediate density lipoprotein	35	30	B100, E	1.006-1.019	25-35
Low-density lipoprotein	50	10	B100	1.019-1.063	18-28
High-density lipoprotein					
(HDL2)	15	5	A-I, A-II	1.063-1.125	9-12
(HDL3)				1.125-1.210	5-9

There is an inverse relationship between density and the size of the lipoproteins. Lipoproteins can be separated on those with atherogenic capacities (with apolipoproteins B100 or E), and those protectives (HDLs). Also, they are distinguished in triglyceride-rich lipoproteins (TRLs) and those that serve to transport cholesterol to the tissues and from these back to the liver (LDL and HDLs). Each lipoprotein is characterized for a type of apolipoproteins, situated in the particle cover, with several functions (see text).
Modified from: Anonymous[6], Gotto A et al.[7]

Table 4: Atherogenic lipids, lipoproteins, apolipoproteins, and markers.[5,9]

Variable/units	Desirable or optimal values
LDL-c, mg/dL	Borderline < 130; desirable < 100; optimal ~50-70
TG, mg/dL	< 150
Non-HDL cholesterol, mg/dL (= TC - HDL-c)	Optimal ~< 100; borderline 100-129
Remnant cholesterol, mg/dL (= TC - LDL-c - HDL-c	Optimal < 19; desirable ~< 30
Apolipoprotein B, mg/dL	Optimal < 60; desirable < 100
VLDL-c, mg/dL	20-25
IDL-c, mg/dL	9-10
Number of particles of LDL, nmol/L	< 1,000
Number of particles of small and dense LDL (LDLsd), nmol/L	< 500
Size of LDLsd, nm	24.2-25.2
ApoB/ApoA quotient	Optimal < 0.6 men; < 0.5 women: desirable < 1 men; < 0.8 women
TC/HDL-c quotient	< 4.5 in men and < 4 in women in primary prevention, and < 4 in men and < 3 in women in secondary prevention
LDL-c/HDL-c quotient	< 3 in men and < 2.5 in women in primary prevention, and < 2.5 in men and < 2 in women in secondary prevention
TG/HDL-c quotient	Optimal < 2; desirable 2-3.9

Abbreviatures as in the text. Non-HDL cholesterol represents the whole set of atherogenic lipoproteins with Apo B. Its measure is particularly indicated in cases of severe hypertriglyceridemia, which prevents the use of Friedewald's formula. Remnant cholesterol is a measure of TRLs: CHY, its remnants, VLDL, and IDL. LDLsd is the number of small and dense highly atherogenic particles, whose proportion increase in hypertriglyceridemic states. The first three quotients of the table simply describe the direct relation between atherogenic cholesterol or apolipoprotein B and ASCVD risk, and the inverse relation between that risk and HDL-c or its main apolipoprotein, A-I. The last ratio, TG/HDL-c is more complex, because signals the state of insulin resistance and its relationship with atherogenic dyslipidemia.

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