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Serum lipids evaluation, is it all done?

Evaluación de lípidos en suero, ¿está hecho todo?

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The structural characteristics of lipids, being organic compounds essentially made up of carbon and hydrogen, give them the ability to be an energy reservoir since, when metabolized, they release nine kcal/g (compared to the four kcal/g released during carbohydrate metabolic degradation to CO_2 and H_2O). Nevertheless, the structure they have makes them insoluble in water. From a metabolic point of view, not interacting with this liquid is an advantage of fats stored as energy repositories, contrasted to carbohydrates. Given the significant interaction of carbohydrates with water, one would require approximately 30 kilograms of carbohydrates to obtain the power generated from only five kilograms of fat; however, their hydrophobicity makes the transport of lipids in biological fluids very difficult.

The chemical structure of these biomolecules is diverse; some examples of such entities are steroids, fatty acids, phospholipids, and glycolipids, among several.

To form part of biological structures or be transported in aqueous liquids such as blood, lipids must be modified or related to molecules that can interrelate with water. An example of those are phospholipids made up of two chains of fatty acids, a phosphate group and a glycerol or sphingosine group. Therefore, this association contains both fragments that attract (hydrophilic) and that repel (hydrophobic) water; that is, they are amphipathic molecules, which allows them to play a critical role in the constitution of cell membranes.

On the other hand, the two main types of fatty molecules in the blood are cholesterol (CHOL) and triglycerides (TGs). With fatty acids, CHOL can esterify; TGs, which should be named triacylglycerides, are constructed by three molecules of fatty acids (saturated and unsaturated) esterified to one of glycerol.

TGs are crucial in the body for energy storage/obtention. To be transported in the blood, these molecules need to mix with proteins, forming complexes known as lipoproteins that help the mobility of lipids in the bloodstream.

During digestion, the intestine releases into circulation the chylomicrons synthesized in the enterocyte. The hepatic delivery of TG-rich, very-low-density lipoproteins (VLDL) into the bloodstream is mainly dependent on TG *de novo* synthesis. This procedure aims to provide TG to peripheral tissues. The elimination of such molecules from VLDL and chylomicrons is mediated by different enzymes and gives rise to smaller sizes fragments and lower consolidation of TGs. They possess distinct thickness since it increases as their magnitude and content of fatty acids decrease. Low-density lipoproteins (LDLs) form in the process, with a high relative aggregation of cholesterol and low in TG.

Most of the LDLs are eliminated; nonetheless, up to 20% of them can infiltrate the vascular wall and can be oxidized and retained in the subendothelial space, initiating local reactions connected to the development of atherosclerosis. All lipoproteins with a diameter of fewer than 70 nanometers can permeate the arterial intima.

Under physiological conditions, the transporter named cholesteryl ester transfer protein (CETP) exchanges lipid molecules between the various lipoproteins. Mature

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HDL-c, whose purpose is to bring cholesterol to the liver for its elimination or reprocessing, exchanges cholesterol with TG-rich lipoproteins (TRGs) as VLDL and remnants, receiving TG in turn. This action, added to the hydrolysis performed by capillary and hepatic lipases, results in smaller and depleted cholesterol LDL particles. Consequently, to obtain similar amounts of cholesterol, smaller LDL besides highly atherogenic elements will be needed.

The clinical evaluation of complex abnormalities in lipid metabolism is generally limited only to assessing the serum concentration of CHOL, TG, and high-density lipoprotein (HDL) with which LDL denseness is calculated. Nevertheless, direct methods can determine LDL aggregation. However, with conventional methods, it is not possible to measure the size and number of LDL units and, therefore, their atherogenic capacity, making the appraisal of the standard lipid profile a very limited procedure.

Multiple efforts have been implemented to solve that limitation. In this regard, to improve the clinical certainty of the risk linked to the concentration of serum lipids, the valuation of non-HDL CHOL, the remainders of cholesterol, or the apolipoprotein B aggregation have been used.

Non-HDL CHOL, in the fasting state, represents all atherogenic lipoproteins, and for that reason, its value has a very good correlation with cardiovascular danger. LDL appears with normal TG concentrated at 70-80% of non-HDL CHOL, permitting an estimate of the cardiovascular risk reasonably. This parameter is useful even in hypertriglyceridemia, except when very high accumulations of TG are present. When TG serum denseness is around or above 500-700 mg/dL, chylomicrons are present alone (type I dyslipidemia) or accompanied with VLDL (type V). But in both conditions, primary, genetic hypertriglyceridemia or secondary to diabetes or insulin resistance syndromes, the higher the TG concentration, the more notable incorporation of particles with lesser or absent atherogenic power (big, floating, parent VLDL, CHYLO, or its vestiges) to the estimation of non-HDL-c, lessening its risk prediction usefulness.

Moreover, the remnants of cholesterol are obtained by subtracting the build-up of HDL and LDL from total cholesterol accumulation; this value loses its relevance in high concentrations of TG (it presents the same disadvantages as the calculation with the Friedwald formula). On the other hand, the determination of Apo B is a very good approximation for the appraisal of the total of lipoprotein elements; it has a highly accurate correlation with cardiovascular events. Conversely, it does not define the relative distribution of lipoproteins; as an example, high aggregations of Apo B can be found in subjects with hypertriglyceridemia or hypercholesterolemia, making the differentiation a complex process.

Considering the complexity of lipid metabolism, the relationships between the diverse lipoprotein particles and the degree of atherogenicity they possess depend on both their amount and magnitude, not only on global lipid concentrations. Consequently, it becomes necessary to have more accurate methods to facilitate the lipoproteins measurements (number of elements and types), better define such variations, and allow a more precise individual cardiovascular peril assessment.

There are alternative possibilities for quantifying lipoproteins that use spectra obtained from them through nuclear magnetic resonance (NMR) techniques. Those methods are based on the physical properties of the methyl groups (-CH3) of cholesterol and TG in the lipoproteins as they «resonate» (vibrate or excite and de-energize) at different frequencies depending on the size of the particle and its content (small molecules do so at lower rates).

The first developed or one-dimensional NMR approach quantifies the various lipoproteins by decomposing the global signal into individual pointers or by statistical means through computational procedures. This method has advantages since it allows to determine the concentration of the lipoproteins more accurately; however, the sizes and numbers of those fragments are still arrived at indirectly.

The second NMR alternative, of more recent development, employs the benefits of resonance together with the diffusion characteristics of the lipoproteins. This type of NMR in two dimensions (NMR-2D) uses the molecules' hydrodynamic properties

(diffusion coefficient). From that, using the Stokes-Einstein equation, the particular extent of each lipoprotein is calculated. Because it depends on its magnitude and complexity, a lipoprotein carried by water on a matrix displaces differently.

This methodology quantifies total cholesterol, LDL (directly), HDL, non-HDL cholesterol, remaining CHOL, and triglycerides, as well as the composition of cholesterol and TG in VLDL, LDL, and HDL. It also determines the dimension and accumulation of particles (large, medium, and small) of the major classes of lipoproteins.

These determinations should admit a better characterization of the patients' risk in the initial evaluations. They also allow for an improved follow-up of persons with insulin resistance, obesity, diabetes mellitus, chronic kidney disease, rheumatoid arthritis, lupus, and all those pathologies in which dyslipidemias can increase the cardiovascular danger.

The search for increasingly accurate diagnostic alternatives should grow the possibility of preventing cardiovascular events in patients. The quantification of the type, size, and quantity of lipoproteins by NMR techniques is an alternative that will make it possible to craft a higher-quality diagnosis and implement enhanced prevention and treatment measures for dyslipidemias.

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