EDITORIAL

HDL lipoproteins: a fluid and changing relationship between quantity and functionality[☆]

Lipoproteínas HDL: una relación fluida y cambiante entre cantidad y funcionalidad

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Those of us who began our professional relationship with the world of plasma lipoproteins and their relationship to cardiovascular disease at the end of the 20th century have lived in a simple and safe world, in which the reference standard was the relationship between the amount of circulating LDL-cholesterol, or Apo B-cholesterol, and cardiovascular risk. For many years our mental framework has been conditioned by the axiom, confirmed in multiple clinical studies with statins and other cholesterol-lowering drugs, that if we reduce the amount of circulating LDL-cholesterol, we reduce the risk of atherosclerotic cardiovascular events. It is the amount of circulating LDL-cholesterol that matters. With this mental framework, applied to the results of epidemiological studies associating an increase in circulating HDL-cholesterol with a lower incidence of cardiovascular accidents and the development of the reverse cholesterol transport theory, we also established the axiom that the higher the amount of circulating HDL-cholesterol, the lower the risk of atherosclerotic cardiovascular accidents.

The 21st century, as in many other fields, has broken this frame of mind and brought us back to the reality of a much more complex and ambivalent world. We can still rely on the predictive value of LDL-cholesterol, but the field of HDL-cholesterol, or HDL in general, has changed substantially. Today we speak not only of the quantity of HDL-cholesterol in circulation, but also of the quality of these HDL, understood as an adequate composition in lipids, apolipoproteins and associated enzymatic endowment that allows the growing list of beneficial properties ascribed to these lipoproteins to be fully manifested, such as their participation in the cellular efflux of cholesterol and the metabolism of remaining lipoproteins, or their anti-inflammatory, antioxidant, antiplatelet aggregation, vasodilator, etc. activity. Among the scientific evidence that has been published in the first two decades of this century and which has led to a paradigm shift in the vision of the role of HDL in cardiovascular pathologies, the following should be highlighted:

- The resounding failure of the bet on drugs inhibiting plasma cholesteryl ester transfer activity as the new revolution in the pharmacological treatment of atherosclerotic cardiovascular disease, despite the huge increase in plasma HDL-cholesterol concentration induced. Even in the case of the only drug that demonstrated a significant reduction in coronary events, anacetrapib, this effect can well be attributed to the reduction in LDL-cholesterol associated with the treatment.[1]

- The publication of robust epidemiological data indicating that very high HDL-Cholesterol levels are associated with an increase in cardiovascular and all-cause mortality, in fact presenting a U-shaped relationship.
- The evidence that, in terms of cardiovascular disease prevention, HDL has a prevailing capacity to facilitate cholesterol efflux from the periphery of the body to the liver, through classical reverse cholesterol transport and by facilitating the metabolism of the remaining cholesterol-rich lipoproteins, the so-called reverse remnant cholesterol transport (RRT).[3]

The study published by Lahoz et al.[4] in the current issue of *Clínica e Investigación en Arteriosclerosis*, focuses on another of the possible pleiotropic effects of HDL as a preventive factor in infectious diseases. Specifically, Lahoz et al.[4] show, in a population at high risk of COVID-19 infection (population aged over 75 years), the existence of an inverse and dose-dependent association between HDL cholesterol concentration and the risk of COVID-19 infection. Moreover, this association is maintained when adjusted for various factors, including cardiovascular risk factors such as diabetes, obesity, hypertension, smoking, etc. Many of these factors are associated with a poor quality of HDL, in terms of its anti-inflammatory and antiplatelet potential, etc., so we can assume that, as the study's conclusions indicate, the reduction in the risk of infection depends decisively on the amount of circulating HDL-cholesterol. Obviously, we still have a long way to go to get a correct picture of the subtle balance between quantity and functional quality as far as the role of HDL is concerned.

Uncited reference

2

References

1. Tall AR, Rader DJ. Trials and tribulations of CETP inhibitors. Circ Res. 2018;122:106–12, http://dx.doi.org/10.1161/CIRCRESAHA.117.311978.
2. Hamer M, O'Donovan G, Stamatakis E. High-density lipoprotein cholesterol and mortality: too much of a good thing? Arterioscler Thromb Vasc Biol. 2018;38(3):669–72, http://dx.doi.org/10.1161/ATVBAHA.117.310587.
3. Kontush A. HDL and Reverse Remnant-Cholesterol Transport (RRT): relevance to cardiovascular disease. Trends Mol Med. 2020;26(12):1086–100, http://dx.doi.org/10.1016/j.molmed.2020.07.005.
4. Lahoz C, Salinero-Fort MA, Cárdenas J, Rodríguez-Artalejo F, Díaz-Almiron M, Vich-Pérez P, et al. Concentración de colesterol-HDL y riesgo de infecciónpor SARS-CoV-2 en personas mayores de 75 años: unacohorte con medio millón de participantes de la Comunidad de Madrid. Clin Invest Arterioscl.