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Editorial

The complexity of the role of HDL-cholesterol

La complejidad del papel del colesterol unido a HDL

Carlos Brotons,[a,b,*] Irene Moral,[a,b] and Johanna Vicuña[b,c]

[a] Unidad de Investigación, Equipo de Atención Primaria Sardenya, Barcelona, Spain
[b] Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, Spain
[c] Servicio de Epidemiología Clínica y Salud Pública, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

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Epidemiological studies, from the first results of the Framingham study to later studies, have shown that there is an inverse association between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular events[1] and that this association is maintained even when low-density lipoprotein cholesterol (LDL-C) is well controlled.[2] These epidemiological results have led to the development of drugs that inhibit the cholesteryl ester transfer protein (CETP) to increase HDL-C, such as dalcetrapib, evacetrapib, and anacetrapib, but none of these has demonstrated the expected causal relationship (as is the case for LDL-C).[3–5] Recently, the results of the Rose trial were presented, indicating that adding another CETP inhibitor (obicetrapib) to classic statin treatment substantially increased the number of patients meeting their LDL-C targets, with reductions in levels of 42% to 51%, while HDL-C increased by 135%, with no observed increase in adverse effects compared with the placebo group.[6] Studies with larger samples are needed to evaluate the effect on cardiovascular morbidity.

Other epidemiological studies, with rather surprising results, showed that the association between HDL-C values and cardiovascular morbidity and mortality remains U-shaped, such that both low values and extremely high values are associated with an increased risk of cardiovascular disease.[7]

More recently, the same authors also observed a U-shaped relationship between HDL-C levels and the risk of hospital admission for any infectious disease.[8] The results of these and other studies indicate that very high HDL-C levels are correlated with higher overall mortality, more than with cardiovascular morbidity and mortality. Possible reasons for this relationship include genetic mutations, abnormal HDL-C functionality, or potential confounding factors, all associated with very high HDL-C levels.[9] These results should be confirmed with other epidemiological studies.

Nowadays, the focus has shifted more to the physiological functions of HDL-C than its concentration. The HDL-C molecule has a series of functions that could be related to cardiovascular disease.[10] One of these is the cholesterol efflux capacity (CEC) of cells, especially macrophages, to the liver and subsequent cholesterol excretion in bile and feces. Just as reverse cholesterol transport is thought to be a protective mechanism against arteriosclerosis, it is reasonable to hypothesize that CEC dysfunction could trigger the process by which plaque formation is accelerated and, consequently, could increase cardiovascular events. To date, no study has demonstrated that an increase in CEC translates into a reduction in cardiovascular events, and therefore it is unclear whether there is a causal relationship.

Another of the functions of LDL-C particles is to protect against LDL-C oxidation, which avoids inflammation of the vessel wall and arteriosclerosis progression. A study evaluating an HDL-C inflammatory index in 193 patients who underwent coronary angiography for suspected acute coronary syndrome reported that patients with evidence of acute coronary syndrome had higher values of this index, indicative of a proinflammatory effect of HDL-C, compared with patients who did not go on to develop coronary disease, demonstrating that the antioxidant capacity of HDL-C is reduced in patients with acute coronary syndrome.[11]

However, to date no studies have demonstrated a causal link between dysfunction of the antioxidant and anti-inflammatory effect and cardiovascular events, although epidemiological studies continue to generate evidence pointing toward such an association. The recent study by Viadas et al.[12] published in *Revista Española de Cardiología* provides a more detailed examination of the effect of current and past leisure-time physical activity and HDL-C functionality in terms of CEC and oxidative capacity in a subsample of individuals from the *Registre Gironí del Cor* (REGICOR) cohort. The authors observed that current (and not past) moderate or intense leisure-time physical activity was associated with higher antioxidant capacity of HDL-C particles, with a maximum benefit with intermediate-low doses (0-400 METs/min/d), and a plateau above this threshold. No association was observed with CEC, and physical activity in the past was not associated with any of the HDL-C functions. Multiple studies had previously demonstrated that physical exercise increases HDL-C[13,14] and that its effect on HDL-C function remains unclear. This study provides further evidence that physical exercise contributes to HDL-C functionality, specifically its antioxidant and anti-inflammatory effect, which could explain the benefits of physical exercise on cardiovascular health. More studies are needed to confirm these results and demonstrate that this function of HDL-C is one that

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* Corresponding author:
E-mail address: cbrotons@eapsardenya.cat (C. Brotons).
@eapsardenya

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truly explains its benefits. Some aspects of HDL-C, such as the U-shaped curve observed in some studies, or the number, size, or ratio of HDL particles per volume of plasma, require further study. It is also true that the routine measurement of HDL-C dysfunctionality is not yet easy or available in clinical practice. Reverse cholesterol transport by CEC can be measured in research laboratories, but not commercially. In future, it would certainly be interesting to be able to measure HDL-C function, especially in patients with substantial residual risk despite well-controlled LDL-C. Before that happens, however, direct evidence of causality is needed, that is, evidence of interventions that demonstrate that enhancing HDL-C functionality improves patient prognosis. Meanwhile, reinforced by the results of the study by Vaidas et al.,[12] we can follow the recommendations on physical exercise of the Department of Health and the World Health Organization adopted by the Spanish Interdisciplinary Committee for Vascular Prevention (*Comité Español Interdisciplinario para la Prevención Vascular;* CEIPV) stipulating engaging in moderate physical activity for at least 150 to 300 minutes per week (or 75 to 150 minutes of vigorous activity or an equivalent combination of the two), reducing periods of sedentary behavior, with active breaks every 1 or 2 hours, increasing active transport, and limiting screen time.[15]

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CONFLICTS OF INTEREST

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