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EDITORIAL

Impaired HDL cholesterol function and high interleukin-1ß levels hold prognostic value after ST-elevation myocardial infarction

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This editorial refers to 'Defective biological activities of high-density lipoprotein identify patients at highest risk of recurrent cardiovascular event', by J. Silvain *et al.*, https://doi.org/10.1093/eurjpc/zwae356.

The role of lipids particles containing apoB lipoprotein in the pathogenesis of atherosclerosis is well established, and the first step in the cardiovascular disease prevention is control of the low-density lipoprotein cholesterol (LDL-C). Nonetheless, despite the correct use of lipid lowering therapies and the management of other cardiovascular risk factors, atherosclerotic cardiovascular disease (ASCVD) remains prevalent.[1] High-density lipoprotein cholesterol (HDL-C) has protective effects against atheroma evolution, promoting the reverse cholesterol transport from the macrophages in the arterial wall, improving endothelial cell function, and protecting LDL-C from oxidative stress.[1] Systemic or even localized inflammation structurally alters HDL-C, impairing its athero-protective functions and its ability to promote cholesterol efflux.[1] However, although it is well-established that low concentrations of HDL-C represent a well-established cardiovascular risk factor,[2] drugs developed to increase HDL-C concentration have failed to reduce major cardiovascular events (MACE).[1] Furthermore, the protective impact of elevated HDL-C does not apply to the elderly,[3] and, paradoxically, extremely high HDL-C levels (>100 mg/dL) are associated with elevated cardiovascular risk, thus leading to the U-shape relationship of HDL-C with cardiovascular events.[2]

In animal models, the enhancement of reverse cholesterol transport is inversely correlated with the evolution of atherosclerosis.[4] In humans, the efficiency of the reverse cholesterol transport can be evaluated with the surrogate parameter of serum cholesterol efflux capacity, which indicates the ability of HDL-C to promote cholesterol efflux.[4] HDL-C-mediated cholesterol efflux represents the first step of reverse cholesterol transport, a main physiological strategy that protects from atherosclerosis. Cell HDL-C efflux capacity may occur through multiple mechanisms, including aqueous diffusion and/or active transport, as the scavenger receptor class B, type I (SR-BI), and the ABCG1 and ABCA1 members of the ATP-binding cassette transporter family.[4]

Cholesterol efflux capacity is a strong predictor of atherosclerosis extent and may represent a useful biomarker of cardiovascular risk.[1] However, HDL-C efflux capacity is impaired in pathological conditions associate with high cardiovascular risk, such as dyslipidemias, chronic kidney disease, diabetes, inflammatory, and autoimmune disease,[1,4] as well as in acute coronary syndrome.[5] Moreover, in the setting of acute coronary syndrome HDL function seems impaired, independently of plasma HDL-C levels: increased myeloperoxidase activity may contribute to a reduction in HDL-C efflux and to an impairment of its anti-inflammatory properties,[5] although other mechanisms may underlie this phenomenon.

Silvain *et al.*[6] previously investigated the role of interleukin (IL)-1ß in patients with myocardial infarction, a pro-inflammatory cytokine involved in the atherothrombosis process, promoting monocyte and leucocyte adhesion to endothelial cells and showing a pro-coagulant activity.[6] Elevated IL-1ß concentration was independently associated with the risk of mortality and recurrence of major adverse cardiovascular events in a cohort of 1398 patients admitted with ST-elevation myocardial infarction.[6]

In the current issue of the Journal, Silvain *et al.*,[7] in a study conducted in 2012 patients with ST-segment elevation myocardial infarction, observe an inverse relationship between cholesterol efflux capacity and circulating levels of the inflammatory marker IL-1ß.[7] Furthermore, Silvain *et al.*[7] identify a subset at very high risk of recurrent cardiovascular events in those patients presenting with impaired cholesterol efflux capacity and high levels of inflammatory markers IL-1ß.[7]

The observation that increased circulating IL-1ß concentration led to a reduction in HDL-C biological function as cholesterol efflux capacity is most relevant in the view of the demonstration that inhibition of IL-1ß by canakinumab led to a reduction in cardiovascular events in patients with stable coronary artery disease with both a history of myocardial infarction and elevated hs-CRP.[8] The improvement of the HDL-C efflux capacity might be achieved by a lifestyle intervention, also considering the beneficial effects of nutraceutical supplementation.[4] On the other hand, within the CLEAR clinical trial, in a time-to-event analysis, colchicine started soon after myocardial infarction did not reduce the incidence of the composite primary outcome of death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization.[9]

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The authors should be commended for underscoring the importance of cholesterol efflux capacity and IL-1ß in the pathogenesis of ASCVD, suggesting their plausible role as a therapeutic target, too. Prospective studies are needed to evaluate how the variation obtained at a second time point of IL-1ß and serum cholesterol efflux capacity after appropriate therapeutic interventions aimed at reducing inflammation and/or improving HDL capacity could better stratify these patients. Though an extensive number of established demographic and clinical confounders was considered in the multi-variable analysis, the addition of simultaneous assessment of plasma B-type natriuretic peptide and peak high-sensitivity troponin I or T should be considered, because of their ascertained role as prognosticators of ventricular remodeling and MACE.

In sum, the studies by Silvain *et al.*[6,7] shed some light on the dangerous combination of inflammation and abnormal cholesterol efflux capacity in patients with ST-elevation myocardial infraction, also indicating a possible therapeutic target. Whether there is a restoration of function of plasma and HDL particles following the acute event should be the object of future studies, evaluating not only male but also female patients.

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Research data are not shared.

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