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Commentary

High-density Lipoproteins (HDLs): biomarkers or bio-actors of abdominal aortic aneurysmal disease?

Olivier Meilhac

*Université de La Réunion, Inserm, UMR 1188 Diabète athérombose Thérapies Réunion Océan Indien (DÉTROI), Plateforme CYROI, 2 rue Maxime Rivière 97490 Sainte-Clotilde, Réunion France
CHU de La Réunion, Allée des Topazes 97400 Saint-Denis, Réunion, France*

Email address : olivier.meilhac@inserm.fr (O Meilhac)

Limits of HDL-C as factor preventing cardiovascular diseases

High-density lipoproteins (HDL) are characterized by their ability to carry out reverse transport of cholesterol from peripheral tissues back to the liver. HDL-cholesterol (HDL-C) concentration has been known for a long time to be inversely correlated with cardiovascular diseases. However, an increasing body of evidence suggests that circulating HDL-C levels may only represent a surrogate marker of atherosclerosis and that these lipoproteins do not participate in the etiology of cardiovascular disease. In fact, Mendelian randomization studies did not support a link of causality and different attempts to increase HDL-C pharmacologically have not reached the expected outcomes¹. This raises the question of HDL functionality rather than HDL-cholesterol concentration. In order to address this point, HDL particles must be isolated from plasma, which represents an important limitation due to the technical burden, since the most recognized method used is sequential ultracentrifugation, which is not a high-throughput technique. In this article of *EBioMedicine*², Martinez-Lopez *et al.* isolated HDLs from a small number of AAA patients (n=27) and they used state of the art proteomic methods to demonstrate modifications on apolipoprotein A1 (apoA1), the major protein of HDLs. This approach cannot be applied to large biobanks of plasma. In the context of large clinical studies, appropriate tools should be developed in order to circumvent this technical limitation, such as a specific ELISA test targeting oxidatively modified tryptophan residues that could allow testing these markers in large cohorts of AAA patients.

Abdominal aortic aneurysm (AAA): an atherothrombotic complication or a lipid-free aortic dilatation?

There is still controversy as to whether AAAs may be considered or not as the result of advanced atherosclerosis of the aortic wall³. The role of lipid accumulation in the first steps of aortic atheroma, that constitutes the substrate for the formation of an intraluminal thrombus, is clearly demonstrated. However, in later stages of this disease, the role of lipids is not established. Therefore, in this context, the relevance of testing HDL function as a mediator for reverse transport of cholesterol is questionable. Indeed, HDLs display pleiotropic effects including antioxidant, anti-inflammatory or anti-protease properties (such as anti-elastase) that may prevent the development of AAA pathology⁴. In their study, Martinez-Lopez *et al.* have shown that apoA1 post-translational modifications are mediated, at least in part, by polymorphonuclear neutrophils (PMNs). PMNs are the most abundant class of leukocytes but are often underestimated in atherogenesis and atherothrombotic complications in favor of lymphocytes. PMNs, particularly abundant in the luminal thrombus of AAA, are likely to be a source of oxidative and proteolytic enzymes that

may produce specific biomarkers reflecting their activation. Martin-Lopez *et al.* could not test the function of HDLs isolated from AAA tissue and the mass spectrometry technique used did not allow them to assess potential proteolytic modifications of HDL-associated proteins (due to the digestion by trypsin prior to MS analysis). This study raises the question of the origin of exacerbated neutrophil activation during the course of AAA pathogenesis. Different triggers may activate PMNs, such as chronic bacterial exposure (i.e. periodontal bacteria ⁵).

A future for HDL in AAA?

Whereas pharmacological increases in HDL-C have failed to prevent cardiovascular disease, repeated supplementation with functional HDL may represent a potential therapy able to limit the expansion of the thrombus in AAA pathology, as demonstrated in a pre-clinical study ⁶. To date, HDL infusion in humans has only been tested in atheromatous and diabetic conditions, taking advantage of the ability of HDL to reduce cholesterol levels and to protect the endothelium ⁷. HDL-based therapy for AAA may represent an option for limiting AAA growth, taking advantage of their pleiotropic effect that may allow tissue healing.

The search for biomarkers in the field of AAA has attracted much attention; they should be able either to detect the disease itself or to reflect its progression. The study by Martinez-Lopez *et al.* revealed that HDL-associated apoA1 is oxidized on Trp residues, potentially due to the activation of neutrophils that release reactive oxygen species and pro-oxidant enzymes, leading to the production of dysfunctional HDL particles. Whereas HDL function may be difficult to evaluate in routine clinical practice, oxidative modification of apoA1 may be more easily quantifiable using antibodies directed against specific epitopes. In addition, proteins other than apoA1 contained in the AAA thrombus probably also undergo such oxidative modifications. Further studies investigating the "proteoxidome" contained within the AAA thrombus, and potentially diffusing into the bloodstream, are necessary to unveil new biomarkers of AAA disease and of its progression.

Disclosure

Dr. Meilhac has nothing to disclose.

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