VASCULAR DISEASE

Cholesterol-efflux capacity might be the key to the protective effects of HDL

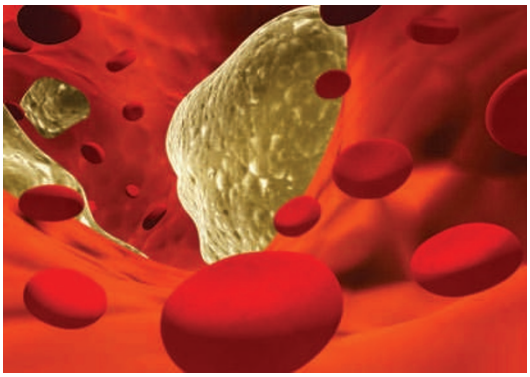
The capacity of HDL to promote cholesterol efflux from macrophages, an important step of reverse cholesterol transport, predicts atherosclerosis and coronary artery disease (CAD), according to findings by Khera *et al.* published in the *New England Journal of Medicine*. Importantly, this effect was found to be independent of circulating HDL-cholesterol levels.

> "The hypothesis that HDL function ... is the key factor linking HDL and CVD is gaining strength"

The link between levels of HDL cholesterol and cardiovascular disease (CVD) is well established, but the mechanisms underlying this association remain elusive. The hypothesis that HDL function, rather than the absolute concentration of this lipoprotein, is the key factor linking HDL and CVD is gaining strength. The study by Khera *et al.* further supports this hypothesis by showing that the capacity of HDL to uptake lipids from macrophages is inversely associated with carotid intima–media thickness and angiographically confirmed CAD, independently of HDL-cholesterol levels.

The investigators measured carotid intima–media thickness, as a surrogate of subclinical atherosclerosis, in 203 healthy participants. A group of 442 patients with angiographically determined CAD and a control group of individuals without CAD determined by angiography were also studied. Cholesterol efflux capacity was quantified in serum samples of all groups. The analysis demonstrated an inverse relationship between cholesterol-efflux capacity and carotid intima–media thickness, which persisted with adjustment for levels of HDL cholesterol or apoliprotein AI; no such relationship was found for HDL-cholesterol levels. Furthermore, cholesterol-efflux capacity was significantly lower in patients with CAD than in the control group without CAD. The levels of HDL cholesterol and apolipoprotein AI, which were significantly lower in the group with CAD, strongly predicted cholesterol-efflux capacity, but they only accounted for <40% of the variation observed between groups.

The researchers also analyzed serum from 39 patients with the metabolic syndrome who had been involved in a trial comparing pioglitazone treatment with placebo, and another group of 99 patients with hyperlipidemia who had been enrolled in a trial comparing statin treatment with placebo. Both pioglitazone and statin therapy were associated with modest increases in levels of HDL cholesterol, but only pioglitazone treatment led to a significant increase in cholesterol-efflux capacity.



The study by Khera *et al.* indicates that cholesterol efflux from macrophages is one of the most-relevant steps of reverse cholesterol transport affecting atherosclerotic burden. As the authors suggest, the influence of size, charge, and protein composition of HDL need to be further explored to understand the role of this molecule in atheroprotection and develop new therapies targeting HDL metabolism and reverse cholesterol transport.

Joana Osório

Original article Khera, A. V. *et al.* Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N. Engl. J. Med.* **364**, 127–135 (2011)