Promoting high-density lipoprotein function via intravenous infusion: the rebirth of apoA-I Milano?

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This editorial refers to ‘A single infusion of MDCO-216 (ApoA-I Milano/POPC) increases ABCA1-mediated cholesterol efflux and pre-beta 1 HDL in healthy volunteers and patients with stable coronary artery disease’, by D.G. Kallend et al., on page 23.

Apolipoprotein A-I (apoA-I) is the major protein component of the high-density lipoprotein (HDL) particles. Higher levels of apoA-I have been associated with a lower cardiovascular risk even among subjects with reduced low-density lipoprotein cholesterol (LDL-C) levels; but, unlike HDL-C, an increase in apoA-I levels in individuals treated with statins has been associated with a lower risk of major cardiovascular events. These and other data have encouraged investigations of apoA-I mimetic compounds or reconstituted HDL particles as a potential therapeutic strategy. ApoA-I Milano (apoA-IM) is a natural variant of human apoA-I identified in individuals in northern Italy, which results from the replacement of arginine by cysteine at position 173 of the apoA-I amino acid sequence; this variation introduces structural changes in apoA-I, allowing the formation of apoA-I homodimers (A-IM/A-IM) and heterodimers with apoA-II, and alters the apoA-I properties, which ultimately may affect HDL function.

The carriers of this variant usually exhibit a lipid phenotype consistent of low HDL-C, low apoA-I, and moderate hypertriglyceridemia; however, despite a lipid profile that may be considered to be pro-atherogenic, apoA-IM seems to confer the carriers protection against the development of atherosclerosis and cardiovascular disease (CVD). These observations have been supported by studies in animals, where the intravenous administration of recombinant apoA-IM has been associated with an improvement of endothelial dysfunction, reduction of vascular lesions, prevention of atherosclerosis progression, plaque regression and stabilization and antithrombotic effects, among others. In humans, a randomized controlled trial in patients with acute coronary syndrome (ACS) found a significant regression of coronary atherosclerosis after treatment with intravenous infusions of apoA-IM/ phospholipid complex (ETC-216, 5 once-weekly infusions), as measured by intravascular ultrasound. In animals, the intramural administration of the same compound (ETC-216) in coronary arteries before stent placement (injury-induced luminal narrowing) significantly inhibited in-stent stenosis through reduction of intimal hyperplasia.

Interestingly, apoA-IM has been associated with an increased capacity of HDL particles to act as extracellular acceptors of cholesterol efflux from cells, which represents one of the first steps in the reverse cholesterol transport. In this way, apoA-IM may enhance the removal of excess cholesterol from the arterial wall and this may explain, at least partly, the protective effect of apoA-IM. Early studies found that cholesterol efflux to sera from apoA-IM carriers was as efficient as sera from control subjects (despite the large reduction of apoA-I and HDL levels in the former), thus suggesting a higher relative apoA-I efflux potential in those carrying the apoA-IM variant. Calabresi et al. further showed that small A-IM/A-IM reconstituted HDL particles were more efficient than the corresponding apoA-I particles as acceptors of membrane cholesterol. Similarly, a single intravenous high-dose of recombinant apoA-IM in high-cholesterol-fed apoE-deficient mice rapidly induced a nearly twofold increase in cholesterol efflux capacity (CEC) compared with controls. And Ciriminno et al. described a decrease in cholesterol content associated with an up-regulation of the arterial wall transporters ABCA1 and SR-RI in aortas from rabbits treated with recombinant apoA-IM.

In the present issue, Kallend et al. report the results of a phase I randomized trial using a single 2-h infusion of highly purified apoA-IM (MDCO-216, apoA-IM/POPC) vs. placebo in 24 healthy volunteers (mean age 26 years, n = 10 males) and 24 stable coronary artery disease (CAD) patients (mean age 62 years, n = 23 males). The administration of MDCO-216 rapidly increased apoA-I levels in a dose-dependent manner and was followed by a change in the lipid profile resembling that previously described in apoA-IM carriers: a decrease in HDL-C and endogenous apoA-I (both more pronounced at higher doses and in CAD patients) and a dose-dependent increase in triglycerides. Additionally, LDL-C decreased...
References