Vinaya Simha and Yogish C. Kudva

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HDL Cholesterol Story Is Dead: Long Live HDL!

It is a great irony that the earliest discovered lipoprotein is also the least well understood. In 1929, Michel Machebouef at the Pasteur Institute in Paris, using salt precipitation techniques, isolated a lipoprotein particle from horse serum composed predominantly of an α-globulin (59%), which we now know to be high-density lipoprotein (HDL) (1). Epidemiological studies in the 1970s, including the Framingham Heart Study, established the strong inverse relationship between HDL cholesterol concentration (HDL-C) and both the incidence and prevalence of coronary artery disease (2,3). The resulting belief about the cardioprotective effects of high HDL-C led to many therapeutic efforts to raise HDL-C using pharmaceutical agents such as niacin, fibrates, and cholesterol ester transfer protein inhibitors that have been largely disappointing (4,5). This has led to a shift in focus from HDL-C to assessment of HDL function, primarily its role in reverse cholesterol transport (4). As many experts have stressed (5), the cholesterol in HDL does not (and cannot) protect, but this does not necessarily reflect on its functional intricacies and importance. Recent evidence does indeed support this greater emphasis on HDL functionality (6) to assess risk for major cardiovascular events, but even this would be a narrow focus. Cholesterol constitutes less than 20% of the HDL molecule, and to truly understand the story of HDL, we need to broaden our focus. The latest iteration of this fascinating tale, presented in this issue of *Diabetes* by Tan et al. (7), does exactly that.

The HDL particle appears to serve a myriad of functions besides reverse cholesterol transport. The well-recognized anti-inflammatory effect has been postulated to play an important role in the pathogenesis of various conditions including obesity, fatty liver disease, diabetes, dementia, osteoporosis, and chronic obstructive lung disease (8). It also affects multiple steps in the response to sepsis including endotoxin release and clearance and response by the macrophages and endothelial cells (9). Similarly, it influences endothelial cell differentiation and function, including nitric oxide production, and may have cytoprotective

and wound healing effects (10). All these functions assume special significance in populations with diabetes mellitus (DM) who are known to have endothelial dysfunction, micro- and macrovascular disease, and poor wound healing. Although there has been considerable research on the nature of dyslipidemia in DM characterized by high triglycerides and low HDL-C, as well as its effect on atherosclerosis, relatively less information is available about the role of HDL function in the pathogenesis of other complications in DM.

In a series of elegant experiments, Tan et al. (7) demonstrate the ability of reconstituted HDL (rHDL) to overcome diabetes-impaired angiogenesis and wound healing. Using a murine hind limb ischemia model, they showed that impaired neovascularization in streptozotocin-induced DM mice was significantly ameliorated by daily infusions of rHDL containing human apolipoprotein A-I (Apo A-I) and a phospholipid. Similarly, topical application of rHDL was shown to improve wound healing. These actions were not noticed in mice without the HDL receptor scavenger receptor class B type 1, thus demonstrating the need for the lipoprotein–receptor interaction. Further, in vitro studies using human coronary endothelial cells helped identify possible mediators and mechanisms of action. High glucose concentrations impair stability of hypoxia-inducible factor-1α, the pivotal transcription factor mediating ischemia-induced revascularization, in addition to decreasing the production and signaling of vascular endothelial growth factors. By decreasing prolyl hydroxylase expression, likely mediated by increased expression of the E3 ubiquitin ligases, rHDL is able to restore hypoxia-inducible factor-1α stability and vascular endothelial growth factor signaling (Fig. 8 in Tan et al. [7]). All these effects were independent of glucose and lipid concentrations. These observations are quite intriguing and seem to suggest that the effects of rHDL may not be secondary to cholesterol transport but a direct consequence of the signaling cascade initiated by Apo A-I scavenger receptor class B type 1 interaction. Further elucidation of this molecular map should help identify other

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Division of Endocrinology and Metabolism, Mayo Clinic, Rochester, MN

Corresponding author: Yogish C. Kudva, kudva.yogish@mayo.edu.

Table 1—Summary of major human studies involving rHDL infusion

Study	Participants (N)	HDL preparation	Dose (protein)	Outcome
Nissen et al. 2003 (11), RCT	123 patients post-ACS	ETC-216: Apo A-I Milano and phospholipid complex	15 or 45 mg/kg, once a week for 5 weeks	Decrease in atheroma volume by IVUS
Tardif et al. 2007 (12), RCT	183 patients with stable CHD	CSL-111: human Apo A-I and phosphotidylcholine complex	40 or 80 mg/kg, once a week for 4 weeks	No change in atheroma volume (IVUS) Improvement in coronary score (angiography)
Gille et al. 2014 (16), open label, phase 2	58 healthy subjects	CSL-112: human Apo A-I and phosphotidylcholine complex	5–135 mg/kg, single dose	Increase in Apo A-I and cholesterol efflux
Tricoci et al. 2015 (17), open label, phase 2	45 patients with stable CHD	CSL-112: human Apo A-I and phosphotidylcholine complex	1.7–6.8 mg/kg, single dose	Increase in Apo A-I and cholesterol efflux
Kootte et al. 2015 (13), open label	7 patients with FHA	CER-001: recombinant human Apo A-I and two phospholipid complex	8 mg/kg, 20 infusions over 6 months	Increase in Apo A-I, HDL-C, and cholesterol efflux Decrease in carotid wall area
Hovingh et al. 2015 (14), open label	23 patients with FH	CER-001: recombinant human Apo A-I and two phospholipid complex	8 mg/kg, 12 infusions over 24 weeks	Decrease in carotid vessel wall area
Tardif et al. 2014 (15), RCT	507 patients post-ACS	CER-001: recombinant human Apo A-I and two phospholipid complex	3–12 mg/kg, weekly infusions for 6 weeks	No change in atheroma volume (IVUS) or coronary artery score (angiography)

ACS, acute coronary syndrome; CHD, coronary heart disease; FH, familial hypercholesterolemia; FHA, familial hypoalphalipoproteinemia; IVUS, intravascular ultrasound; RCT, randomized clinical trial.

potential targets for intervention, although it must be borne in mind that the pharmacological effects of high-dose Apo A-I infusion does not necessarily imply the same normal biological role for the HDL molecule.

rHDL infusion has been previously shown to ameliorate atherosclerosis (Table 1). Limited data show the potential of rHDL containing the mutant Apo A-I Milano to reduce atheroma volume (11), and studies using other rHDL preparations containing normal human Apo A-I such as CSL-112 are under way. Weekly infusions of an earlier form of this compound, CSL-111, did not have significant effects on atheroma volume in the Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) trial (12). CER-001 is another rHDL preparation shown to improve cholesterol efflux, although clinical studies have yielded mixed results (13–15). To a large extent, these are proof-of-concept studies, and the feasibility of using rHDL infusions to treat a chronic condition such as coronary artery disease needs to be assessed even if future studies show positive results on atheroma regression. However, the findings reported by Tan et al. (7) raise other therapeutic possibilities such as those regarding the treatment of vascular and nonhealing ulcers, where limited duration of therapy may still be effective for ulcer healing and potential limb salvage. We currently have limited pharmacological options for the treatment of peripheral vascular disease, and HDL-based therapies may fill a big void. Although the use of rHDL infusions or local application to treat diabetic foot ulcers is still not on the horizon, we are certainly uncovering newer and exciting chapters in the HDL story.

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