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An increasing body of evidence suggests that disturbed HDL metabolism increases the risk of cardiovascular disease (CVD).\(^1\) HDL metabolism is central to reverse cholesterol transport (RCT), in which excess cholesterol from peripheral tissue is returned to the liver for extracorporeal elimination. HDLs also have non–RCT functions including antiinflammatory, antioxidant, and antithrombotic properties. These may relate collectively to the apoA-I content of HDL particles. A number of therapeutic approaches that target HDL metabolism may be useful in preventing and regressing atherosclerosis and coronary disease.\(^2-^3\)

Among lipid-regulators, niacin (nicotinic acid, vitamin B3, pyridine-3-carboxylic acid) is the most effective therapeutic agent presently available for elevating HDL-cholesterol and apoA-I. Notwithstanding issues with tolerability, niacin has long been available for treating atherogenic dyslipidemias. Data from several clinical trials collectively demonstrate that niacin alone or in combination with other agents, including statins, can reduce cardiovascular events and apoA-I concentration by several mechanisms involving reductions in plasma VLDL-triglyceride concentrations by several mechanisms involving reductions in plasma VLDL-triglyceride concentrations and in the expression, activity, and mass of CETP; there was also a non–dose-dependent reduction in hepatic lipase activity. Using exogenously radiolabeled \(^{125}\)I-apoA-I and monoeponential analysis, they reported that niacin dose-dependently decreased the clearance of apoA-I from plasma (associated with reduced uptake by the kidney), but did not alter the hepatic secretion of apoA-I nor the biliary and fecal excretion of cholesterol. With high dose of niacin (1180 mg/kg/d), the decrease in plasma triglycerides (+77\%) was associated with a commensurate increase in the residence time of HDL-apoA-I (+89\%). The kinetic findings generally concur with previous in vitro studies in HepG-2 cells, and suggest that the main mechanism for the elevation in plasma apoA-I concentration with niacin involves decreased clearance of apoA-I related to a primary reduction in the expression and activity of CETP.\(^6\)

These data from van der Hoorn et al have to be placed within the context of the complexity of the bioregulation of the HDL system. The authors postulated that by inhibiting the hormone-sensitive lipase via the niacin receptor GPR109A in adipose tissue, niacin decreases triglyceride lipolysis and thereby the release of free fatty acid (FFA) from adipocytes. The decreased flux of FFA to the liver could inhibit triglyceride synthesis and subsequent hepatic secretion of larger size VLDLs. Consistent with previous studies, they suggested that the increase in HDL-cholesterol may be a consequence of reduction in the pool of plasma VLDL (the acceptor of CETP-mediated HDL-CE transfer) that is available for the heteroexchange of neutral lipids (cholesterol and triglycerides) under the action of CETP. Their demonstration in this animal model that hepatic lipase activity was inhibited by niacin could also contribute to the formation of larger, CE enriched HDL particles that are cleared more slowly from the circulation. However, these postulates have to be weighted against the lack of data presented on the kinetics of both FFA and VLDL. Beyond the impact of the therapeutic decrease in triglyceride substrate on CETP activity, the reduction in hepatic cholesterol content with niacin reported in the present study could also decrease the hepatic expression of CETP via a liver X receptor (LXR) response element on the CETP promotor.\(^7\) However, in other studies, niacin has not been found to decrease plasma CETP activity.\(^8\) Moreover, recent data indicate that niacin may directly inhibit hepatocyte diacylglycerol acyltransferase-2 (DGAT-2), a key enzyme in triglyceride synthesis.\(^9\) There is also good evidence that in HepG-2 cells, niacin retards the hepatic catabolism of apoA-I via the “HDL holoparticle catabolism receptor” pathway and not by the SRB1 pathway,\(^10\) consistent with the absence of effect of niacin on expression of SR-B1 in the study by van der Hoorn et al.\(^5\) The precise role that the renal cubulin-

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**Editorial**

**Of Mice and Men**

**Blowing Away the Cobwebs From the Mechanism of Action of Niacin on HDL Metabolism**

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1892
**A Reference State**

Adipose tissue

Liver

Adipose tissue

**B Insulin Resistant State**

**C Potential mechanism of action of niacin**

Figure. Simplified scheme depicting lipid and lipoprotein metabolism (fatty acid, triglyceride, VLDL, and HDL) in the reference state (A), insulin resistant state (B), and potential mechanism of action of niacin (C). The proposed effect of niacin on VLDL and HDL kinetics is based on the results of both animal and human models. CE indicates cholesteryl esters; CETP, cholesterol ester transfer protein; DG, diacylglycerol; DGAT-2, DG acyltransferase-2; FCR, fractional catabolic rate; FA, fatty acid; HDL, high-density lipoprotein; HSL, hepatic lipase; niacin receptor, G protein–coupled receptor GPR109A; PR, production rate; SR-BI, scavenger receptor-B1; TC, total cholesterol; TG, triglyceride. VLDL, very-low density lipoprotein. For further details see text. ↑ indicates increase; ↓, decrease. The relative extent to which liver and kidney contributed to the catabolism of HDL-apoA-I remains unclear.
megalin receptor complex plays in the mechanism of niacin in delaying the clearance of apoA-I from plasma remains to be investigated.

Mouse models have been used widely to evaluate the impact of therapies on atherosclerosis and lipoprotein metabolism. Why did the authors use the E3LCETP mouse model? First, by inserting the human CETP transgene, they could investigate, as in another mouse model,\textsuperscript{11} whether CETP modulates the effect of niacin on HDL metabolism. Second, unlike the APOE\textsuperscript{−/−} and LDLr\textsuperscript{−/−} models which exhibit extremely elevated plasma cholesterol concentration on a high-fat diet (>25 mmol/L), the E3LCETP mouse tends to simulate a more human-like lipoprotein profile (plasma triglyceride \(\approx 3\) mmol/L and cholesterol \(\approx 12\) mmol/L) and may be more sensitive to lipid-lowering therapies.\textsuperscript{12} However, genetic-manipulated mouse models do not strictly reflect the physiology nor pathophysiology of human lipid and lipoprotein metabolism.

It should also be noted that the doses of niacin used in the present and in another experimental study are substantially higher than those used clinically in treating human dyslipidemias (1 to 2 g/d), potentially limiting the translational value of the data.\textsuperscript{5,11} The authors argued that the experimental doses are clinically relevant because of the higher metabolic rate of mice (5 to 10 times) compared with humans. The validity of this claim is, however, questionable in the absence of data on the comparative pharmacokinetics of niacin.

How do the findings by van der Hoon et al compare with kinetic studies in humans? Using exogenously radiolabeled \(^{125}\text{I}\text{-apoA-I}, \text{in normolipidaemic subjects 3-week treatment with niacin (3 g/d) has been shown to increase plasma apoA-I by decreasing its catabolism.}\textsuperscript{13,14}\) However, a recent endogenously labeling isotope study by Lamon-Fava et al reported that in men with combined hyperlipidemia featuring low HDL-cholesterol at baseline, 12-week treatment with niacin (2 g/d) significantly increases HDL-apoA-I concentration by increasing the production of apoA-I.\textsuperscript{8} Discrepancies among the aforementioned studies might be attributable to different experimental models, subject characteristics (gender and baseline HDL-cholesterol) and study design (dose and duration of treatment), modeling of the data (monoeponential versus multicompartmental analyses), and study protocols (radiolabeling versus stable isotopic techniques).

Reverse cholesterol transport is a major mechanism by which HDL protects against atherosclerosis. The present data did not find a significant effect of niacin on biliary and fecal cholesterol excretion. This suggests that niacin treatment may not elicit a net extracorporeal flux of cholesterol, despite significantly increasing plasma HDL-cholesterol and apoA-I concentrations. This notion needs further investigation. Voogt et al recently described a novel stable isotope method for assessing cholesterol efflux and transport from tissues in humans (see deGoma et al\textsuperscript{15}) and application of this test, and other pertinent measures of HDL functionality, to the effects of niacin would be of interest.

The efficacy of niacin in correcting atherogenic dyslipidemia does not only depend on its impact on HDL, but also on the simultaneous reduction in triglycerides, LDL-cholesterol, apoB and Lp(a) concentrations. Further investigation of the integrated mechanism of action of niacin on human lipoprotein transport is warranted, given divergent data on the effect of this agent on the secretion and clearance of VLDL.\textsuperscript{5,15,16}

Beyond lifestyle modifications, niacin is potentially the most clinical useful agent in treating atherogenic dyslipidemia in subjects with insulin resistance syndrome. The Figure shows how VLDL and HDL transport is perturbed by insulin resistance and how niacin may potentially correct these abnormalities. Hypertriglyceridemia and low HDL-apoA-I in insulin resistance may be caused by a combination of overproduction of VLDL-apoB-100, decreased catabolism of VLDL-apoB-100, and increased catabolism of HDL-apoA-I particles (Figure 1b). These abnormalities may be consequent on a global metabolic effect of insulin resistance that increases the flux of FFA from adipose tissue to the liver, the accumulation of fat in the liver, increased hepatic secretion of triglycerides, and remodeling and overcatabolism of HDL particles in the circulation. Based on the findings of van de Hoorn et al, and on recent data from in vitro and human studies, niacin may correct abnormalities in this system by inhibiting triglyceride lipolysis and subsequent hepatic triglyceride synthesis for VLDL production, as well as by increasing the production of apoA-I and decreasing CETP-mediated heteroexchange of neutral lipid between HDL and VLDL that slows the clearance of HDL-apoA-I (figure 1C). As we have argued elsewhere,\textsuperscript{17} however, the optimal antiatherogenic effect of a given therapeutic agent on HDL metabolism may be to increase HDL-apoA-I transport and concentration with unchanged or increased catabolism, reflecting an accelerated rate of RCT.

Niacin treatment is likely to be most frequently used in combination with statins. However, the kinetic effect of this combination on HDL metabolism in MetS has not yet been investigated. Niacin added to a statin increase the concentration of larger size α1-HDL and this may be associated with less progression of coronary atherosclerosis.\textsuperscript{18} Whether niacin alone or in combination with statins decreases cardiovascular events awaits further confirmation in the ongoing AIM-HIGH and HPS-THRIVE trials.\textsuperscript{4} Direct competitive inhibitors of CETP elevate HDL to a greater extent than niacin, but their clinical use has been seriously questioned by the ILLUMINATE study.\textsuperscript{19} However, this may relate to a specific, off-target pressor effect of torcetrapib that is not a feature of other direct CETP inhibitors.\textsuperscript{20} Niacin does not per se elevate blood pressure, but like CETP inhibitors delays the clearance of HDL-apoA-I.\textsuperscript{21} Finally, the clinical success of niacin as a treatment for dyslipidemia and atherosclerosis also depends on use of preparations, such as extended release forms with or without a prostaglandin (PG) D2 (PGD2) receptor antagonist (laropiprant), that significantly but do not totally diminish the risk of flushing, an end point that was not reported in the E3LCETP mouse model!\textsuperscript{15}

Disclosures

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References


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