Editorial

Lp A-I and Niacin
New Views of an Antiatherogenic Duo

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Increasing evidence from epidemiological, clinical, and basic mechanistic studies supports the importance of HDL in preventing or even reversing atherosclerosis. The well-known structural and compositional diversity of HDL subfractions seems to be an important, if still somewhat unclear, factor in the atheroprotective potential of a given HDL particle. Perhaps as important as the parameter of particle size is that of apolipoprotein content of HDL. HDL particles which lack apo A-II (Lp A-I) appear to associate with reduced atherosclerosis risk⁴ and are reported to be better cholesterol acceptors in some,²,³ although not all studies⁴ as compared with HDL with apo A-II (Lp A-I/A-II).

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Niacin generally is considered the most effective agent for raising HDL levels, typically increasing HDL-C by 30%.⁵ The mechanism of this effect has been shown, by in vivo human turnover studies, to be a decrease in its fractional catabolic rate.⁶,⁷ Interestingly, despite the earlier clinical importance of both niacin and Lp A-I levels, the impact of the former on the latter has been little studied. One earlier intensive study of a small number of subjects showed that niacin selectively raised Lp A-I levels while Lp A-I/A-II declined somewhat,⁸ but this question appears not to have been further tested in almost two decades since. Gemfibrozil also is effective in raising HDL levels, although generally less than half as much as niacin.⁹ The major HDL-raising mechanism of gemfibrozil appears to be an increase in production of apo A-I, as demonstrated by Sakai et al.¹⁰ in vivo and by Jin et al.¹¹ in vitro. Surprisingly, the effect of gemfibrozil on levels of Lp A-I and Lp A-I/A-II has not been reported, to our knowledge.

Sakai and coworkers¹² have now addressed some of the gaps in our understanding of the effects of niacin and gemfibrozil on HDL in their report titled “Niacin but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL-cholesterol” in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology. They present data from three interrelated experiments in which effects of these agents on HDL subfractions Lp A-I and Lp A-I/A-II were explored in vivo and in vitro. In their in vivo study, they confirmed the earlier finding⁴ that niacin selectively increases Lp A-I levels but has no consistent effect on Lp A-I/A-II. We interpret these data to suggest that the relatively dramatic rise in total HDL with niacin may actually underestimate its potential antiatherogenic effect. Nevertheless, despite the fact that gemfibrozil has now been shown to lack a specific effect on Lp A-I,¹² it appears to prevent atherothrombotic events⁹,¹³ roughly comparable to niacin¹⁴,¹⁵ and its ability to prevent atherosclerosis may even relate to the modest degree of HDL-C increase.¹⁶,¹⁷ Thus, a selective rise in Lp A-I may contribute but clearly is not essential to atheroprevention.

In one of their two in vitro experiments, Sakai and coworkers¹² showed that niacin selectively reduced the uptake of Lp A-I apolipoprotein by hepatoma (Hep G2) cells, while in contrast gemfibrozil had no effect on the apolipoprotein uptake of either HDL subspecies. These data suggest that differences in effects on hepatic uptake of Lp A-I between niacin and gemfibrozil may account for differences in their effects on the overall apo HDL FCR and on Lp A-I and HDL levels. Unfortunately, the authors did not provide data on HDL apolipoprotein catabolism, a crucial omission in light of the fact that the uptake of HDL apolipoproteins often does not lead to their catabolism, especially in steroidogenic cells.¹⁹ Also unfortunate is the lack of absolute protein uptake data, making it impossible to compare uptakes of Lp A-I with Lp A-I/A-II, or protein uptake with CE uptake. Lp A-I seems to have a faster overall FCR in vivo than Lp A-I/A-II,²⁰ but no data seem to be available regarding effects of niacin or gemfibrozil on turnover of these subfractions in humans. Meanwhile, the apparent concordance between the decrease in the in vitro uptake and increased in vivo levels with niacin may further establish Hep G2 cells as a good model system for studies of effects of medications on HDL in humans.

The other in vitro part of the current report¹² tested for effects of niacin and gemfibrozil on a likely crucial aspect of human HDL-mediated lipid metabolism, the uptake of [¹⁴C]-HDL-CE by hepatocytes, as modeled by Hep G2 cells. Unesterified cholesterol from HDL has been shown to be an important source of hepatic cholesterol in vivo in humans,²¹ as also likely HDL-CE, although its metabolism in humans has been little studied.²² Kashyap’s group previously reported that niacin caused a modest but statistically significant 15–17% reduction in Hep G2 uptake of apolipoproteins from whole immunosolated HDL.¹⁸ Confusingly, they called this whole HDL “Lp A-I,” even though it was a mixture of both the HDL subfraction conventionally termed “Lp A-I” (HDL lacking apo A-II) and Lp A-I/A-II. In the current study,¹² they tested these subfractions separately and found that Hep G2 uptake of apolipoproteins from Lp A-I also was decreased by 15–17% by niacin (the same effect as seen earlier on whole HDL), although it had no effect on uptake of Lp A-I/A-II apolipoproteins. Meanwhile, gemfibrozil had no effect on apolipoprotein uptake of either HDL subfraction. Interest-

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ingly, the effect of niacin did not translate into a significant change in Lp A-I-CE uptake with that agent, just as it had not in the previous report.18 There was, however, a strikingly higher [\( ^{3}H \)-CE uptake from Lp A-I than from Lp A-I/A-II. This difference is consistent with other studies showing that Lp A-I is better than Lp A-I/A-II both as a lipid donor to steroidogenic tissues (for a review, see Trigatti et al22) and as a lipid acceptor from peripheral cells.2,3 The concordance of these data and the apparent antiatherosclerotic effect of Lp A-I (versus Lp A-I/A-II) favor HDL-mediated reverse cholesterol transport as an important mechanism of atheroprotection.

Unfortunately, Sakai and coworkers12 did not report any details of possible mechanisms by which the apolipoprotein uptake or CE transfer occurred, leaving many important questions unanswered. Could HDL apolipoprotein uptake be related to a previously described HDL cell-surface receptor?24 A second cell-surface protein, SR-BI, binds HDL on liver and steroidogenic cells and may play an important role in lipid transfer between HDL and the liver.23,25 A third protein, hepatic lipase, is also prevalent on the hepatocyte cell surface and is described to enhance the ability of SR-BI to promote lipid transfer from HDL to hepatocytes.26 Niacin in combination with simvastatin has been shown to lower hepatic lipase activity,27 but the effects of either agent alone are unclear. Also, apo A-II may either decrease28 or increase29 HDL activity, and the relative activities of Lp A-I and Lp A-I/A-II as substrates for this enzyme remain unknown. Hep G2 cells make active hepatic lipase in amounts sufficient to be detected,30 at least in earlier passages, which may alter their HDL metabolism. Was the HDL-CE transfer to Hep G2 cells, as examined by Sakai and coworkers,12 regulated by one or more of these cell-surface proteins? By what mechanism might niacin have reduced the uptake of HDL apolipoprotein but not of CE? What cellular factors mediate the differences between Lp A-I and Lp A-I/A-II in apolipoprotein and CE metabolism?

The fact that the Lp A-I and Lp A-I/A-II used in the in vitro experiments were isolated from untreated subjects leaves open the question whether niacin or gemfibrozil may cause qualitative changes in either particle, which may affect their interaction with hepatocytes. Another key question is the adequacy of the cell culture model. Hep G2 cells are a convenient and reasonable model system for native human hepatocytes, but they do differ genotypically and phenotypically from their nontransformed counterparts. How might these differences have affected the in vitro study results? Furthermore, even native hepatocytes in primary culture are likely to differ in many ways from the liver as a whole in an intact organism, as a result of changes during isolation and culture. It will be important to verify the interesting findings of Sakai and coworkers12 by using primary cultures of native human hepatocytes, and in vivo, as possible.

Despite these drawbacks, the report of Sakai and coworkers12 should increase attention to the use of niacin in a clinical setting. Other recent events are also increasing the potential importance of niacin in clinical treatment. Recent reports by us5 and others31 suggest that niacin is far less harmful to glucose control in diabetic and nondiabetic patients than previously thought. Also, the development of a safer extended-release formulation32 makes routine niacin use more feasible. Furthermore, the efficacy of niacin in raising HDL levels is of greater importance in light of recent concerns about another class of HDL-raising drugs, oral estrogens. The recently released AHA advisory that nearly completely proscribes estrogen therapy for CHD prevention in postmenopausal women33 might be criticized for too broadly extrapolating from essentially one relatively narrow clinical trial (HERS, which studied oral estrogen/progesterin in secondary atheroprevention in older postmenopausal women).34 Nevertheless, the obvious need for increased caution with estrogen replacement therapy makes the already short list of practical HDL-raising agents shorter still and increases the relative utility of niacin.

The report by Sakai and coworkers12 sheds valuable light on a complex and important subject and may further encourage clinical use of niacin. As is always the case, however, this study raises more questions than it answers. Clinical trial data relating pharmacologic increases in HDL levels with atherosclerosis event–reduction continue to accumulate, as do data regarding antiatherosclerotic mechanisms of HDL. More frequent and more aggressive treatment of HDL deficiency already may be warranted in selected high-risk cases; meanwhile, the need remains for further exploration of HDL metabolism and development of HDL-raising therapy.

References


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