High-Density Lipoprotein
A New Therapeutic Target for Glucose Intolerance?

Stefan P. Mortensen, DMSc; Robert Boushel, DSc

For >30 years it has been known that elevated high-density lipoprotein (HDL) cholesterol is preventative against the development of atherosclerosis.1 Besides its role in cholesterol removal, HDL is also an antioxidant,2–5 it inhibits inflammation1 and thrombosis,3 and also stimulates endothelial nitric oxide6 and prostacyclin7 release. In addition to these cardiovascular protective actions, recent research findings have elucidated the important role of HDL and its constitutive apo-protein components for glucose metabolism. HDL can lower blood glucose levels by mechanisms that include stimulation of insulin secretion from pancreatic β-cells8,9 and activation of the AMPK signaling pathway in skeletal muscle.8,10 These findings have opened up for an important area of investigation, especially given the increasing prevalence of metabolic disorders such as type 2 diabetes mellitus.

The recent work by Lehti and colleagues11 appearing in this issue of Circulation uses a mouse model of apolipoprotein A-I (ApoA-I; the major protein component of HDL) knockout and overexpression (ApoA-I tg) to examine loss and gain of function effects on fasting plasma cholesterol, lipoprotein profile, glucose homeostasis, body composition, and exercise performance in vivo. From tissue extracts they examine liver and muscle glycogen, muscle AKT phosphorylation, mitochondrial function, and protein expression of mitochondrial ATP synthase subunits. In parallel experiments in C2C12 myoblasts incubated in glucose, they examine the dose–response effect of HDL on glycolytic rate and mitochondrial function (as well as the effects of glucose combined with LDL, phospholipid vesicles and ApoA-I). There are several novel and exciting findings in this study. First, ApoA-I KO mice exhibited metabolic impairments including elevated fasting glucose and HbA1-C, lower lean body mass, reduced muscle mitochondrial respiratory capacity, and a decrease in endurance exercise capacity compared with age-matched controls. Second, overexpression of ApoA-I (ApoA-I tg), which induced a higher total cholesterol level than in wild type (WT), ameliorated all of these effects and improved non–insulin-dependent glucose homeostasis beyond WT along with a higher lean body mass and higher expression of mitochondrial ATP synthase protein. Third, in C12C2 myoblasts incubated in glucose, HDL treatment directly stimulated glycolytic rate and mitochondrial respiration at high doses and this effect was mimicked by ApoA-I treatment alone in the same preparation. Fourth, when ApoA-I tg mice were compared with WT after an 8-week interval to reflect the influence of age, exercise endurance capacity was much better preserved. Finally, the authors also examined the link between fibroblast growth factor-21 (released from the liver and other tissues) and adipose tissue lipolysis12 and mitochondrial function and found that overexpression of ApoA-I prevents diet-induced obesity in sedentary mice in association with decreased hepatic and circulating fibroblast growth factor-21.

A number of intriguing questions for further investigation emerge from this study. The authors’ observation that HDL may have direct effects on mitochondrial function in both skeletal muscle and adipose tissue is of great interest. Following up on this and a previous study,1 a key question of interest is whether elevating HDL (eg, HDL infusion into the circulation) has an acute effect on muscle oxygen uptake, glucose, and FFA oxidation at rest and during exercise in humans. This approach would ascertain whether their concentration-dependent findings in myoblasts also apply to in vivo conditions. Based on the finding that ApoA-I overexpression prevents diet-induced obesity in sedentary mice, it would be of interest to determine whether this effect is also observed in humans when HDL is chronically elevated. Furthermore, is there a synergistic effect of elevated HDL and exercise training on glucose metabolism and homeostasis independent of obesity? The finding that ApoA-I overexpression attenuates the decline in endurance exercise capacity compared with WT over the 8-week study period also merits investigation in humans and has potentially important implications for healthy aging. In addition to these key areas this study also advances an important experimental model in which to further investigate the causality between mitochondrial function, insulin resistance, and type 2 diabetes mellitus. The authors’ view and current findings implicate mitochondria as a contributing causal factor in this ongoing debate. The strong link between a lower mitochondrial function and glucose intolerance in the ApoA-I KO mice supports this view. However, respiratory control ratio estimates from these data also suggest that mitochondrial volume is significantly reduced in the KO mice, supporting the common finding of a lower expression of mitochondrial
accompanying dysregulated glucose metabolism. Further investigation related to the finding that ApoA-I overexpression improved glucose metabolism above that of WT without an elevated mitochondrial respiratory capacity may provide insight on this important question. The link between HDL-mediated induction of AMPK is of particular interest for elucidating the role of elevated HDL on fatty acid oxidation and mitochondrial biogenesis in skeletal muscle. Along these lines, the higher expression of mitochondrial ATP synthase subunit protein in ApoA-I tg is an important finding and points to a determination of the functional significance on mitochondrial ATP synthesis rates in humans.

In closing, the study by Lehti and colleagues will undoubtedly spur much interest in further elucidating the mechanistic links between HDL and energy metabolism and the importance of these pathways for the prevention and treatment of type 2 diabetes mellitus. A key question is how these findings in rodents apply to humans, especially considering the different lipoprotein profile in rodents versus humans related to the cholesterol ester transfer protein deficiency in rodents. A short-term increase in HDL can lower plasma glucose in type 2 diabetics, but the effect of chronic increases in HDL on glucose metabolism is unknown. Large clinical trials investigating the long-term effect of HDL-raising agents are therefore needed as well as in-depth mechanistic trials. With regard to the latter, an unresolved area is how HDL affects tissue perfusion and consequently glucose availability via its effect on endothelial nitric oxide and prostacyclin formation, especially given the present observation that HDL improves endurance performance. If the metabolic effect of chronic increases in HDL can be confirmed in humans, the therapeutic potential of HDL-raising agents to both prevent and treat cardiovascular disease and manage metabolic disorders in type 2 diabetes mellitus is promising.

Sources of Funding

The Copenhagen Muscle Research Center is supported by a grant from the Capital Region of Denmark. The Center of Inflammation and Metabolism (CIM) is supported by a grant from the Danish National Research Foundation (#02-512-55).

Disclosures

None.

References


Key Words: Editorials • glucose • metabolism • muscles • type 2 diabetes mellitus
High-Density Lipoprotein: A New Therapeutic Target for Glucose Intolerance?
Stefan P. Mortensen and Robert Boushel

Circulation. 2013;128:2349-2350; originally published online October 29, 2013;
doi: 10.1161/CIRCULATIONAHA.113.006345
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/128/22/2349

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/