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

Running title: Mortensen et al.; HDL and glucose metabolism

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For over 50 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\(^2\-3\), it inhibits inflammation\(^4\) and thrombosis\(^5\) and also stimulates endothelial nitric oxide (NO)\(^6\) and prostacyclin\(^7\) release. In addition to these cardiovascular protective actions, recent research findings have elucidated the important role of HDL and its constitutive apoprotein components for glucose metabolism. HDL can lower blood glucose levels by mechanisms that include stimulation of insulin secretion from pancreatic \(\beta\)-cells\(^8\,9\) 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.

The recent work by Lehti and colleagues\(^11\) 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 \(\text{tg}\)) 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, PLV 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 muscle glucose uptake, elevated liver triglycerides, lower lean body mass, reduced muscle mitochondrial respiratory capacity, and a decrease in endurance exercise capacity compared to age matched controls. Second, overexpression of ApoA-I (ApoA-I \(\text{tg}\))
which induced a higher total cholesterol level than in 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 to WT following an 8 week interval to reflect the influence of age, exercise endurance capacity was much better preserved. Lastly, the authors also examined the link between FGF-21 (released from the liver and other tissues) and adipose tissue lipolysis and mitochondrial function and found that overexpression of ApoA-I prevents diet-induced obesity in sedentary mice in association with decreased hepatic and circulating FGF-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, a key question of interest is whether elevating HDL (e.g., 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 if 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 to 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. 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 support 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 mitochondria 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 colleagues11 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. 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 (CETP) deficiency in rodents. A short term increase in HDL can lower plasma glucose in type 2 diabetics8, 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. In regards to the latter, an unresolved area is how HDL affects tissue perfusion and consequently glucose availability via its effect on endothelium NO and prostacyclin formation\(^\text{13}\), 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 is promising.

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