The emerging role of HDL in glucose metabolism

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The association of low plasma levels of high-density lipoprotein (HDL) with states of impaired glucose metabolism and type 2 diabetes mellitus is well established, but the mechanistic links remain to be fully elucidated. Recent data from our laboratory (Drew *et al.*, 2009) and others suggests that HDL directly influences glucose metabolism through multiple mechanisms. This presentation will discuss the emerging evidence and mechanisms by which HDL modulates glucose metabolism in the context of the well established actions of HDL.

Low HDL has been traditionally considered an atherosclerotic risk factor on the basis of convincing epidemiology, demonstrating an association with negative cardiovascular outcomes, even at very low levels of LDL. The process of cholesterol removal from peripheral cells such as macrophages, for transport to the liver and subsequent excretion is termed reverse cholesterol transport, and is generally viewed as the most important anti-atherosclerotic action of HDL. However, in addition to reverse cholesterol transport, HDL is now known to convey an impressive spectrum of protective properties including inhibition of inflammation, oxidation and thrombosis, as well as vasodilatation *via* nitric oxide.

Recent experimental and clinical developments linking HDL to glucose metabolism suggest yet another beneficial action of HDL that may have relevance to diabetes. We have shown that HDL elicits reductions in blood glucose in patients with type 2 diabetes (Drew *et al.*, 2009) which likely occurs through multiple actions including stimulation of pancreatic β-cell insulin secretion (Drew *et al.*, 2009; Fryirs *et al.*, 2010) and increased glucose uptake into skeletal muscle *via* activation of the AMP-activated protein kinase (AMPK) signaling pathway (Drew *et al.*, 2009). In addition, given the established role of lipid accumulation and inflammation in the pathogenesis of type 2 diabetes, it is highly likely that the reverse cholesterol transport and anti-inflammatory actions of HDL in metabolic tissues contribute to improved insulin sensitivity and thus glucose homeostasis. We therefore hypothesized that HDL may improve insulin sensitivity *via* lipid removal and anti-inflammatory actions in macrophages associated with excess adiposity/ectopic lipid deposition. A variety of macrophage cell models including RAW 264.7 (mouse), THP-1 (human) and primary human macrophages from healthy participants were incubated separately with an acetylated LDL lipid challenge and then co-treated with either HDL (50μg/mL) or vehicle for 18 hours. Fresh conditioned media from macrophage cultures was applied (1:10) to primary human skeletal muscle cell cultures derived from 5 unmedicated patients with type 2 diabetes for 24 hours and insulin-mediated glucose uptake (2-deoxyglucose) measured. In all models, acetylated LDL treatment reduced insulin-mediated glucose uptake to basal levels and co-treatment with HDL restored insulin mediated glucose uptake to control levels. These data suggest that macrophage inflammation associated with excess/ectopic adiposity is reduced by HDL and these effects may contribute to improved insulin sensitivity and glucose homeostasis.

Research in this area is in a preliminary phase, with the potential for HDL elevation to provide metabolic protection yet to be proven in a chronic context. However, findings to date provide fertile ground for mechanistic speculation regarding links between HDL and glucose metabolism in the context of diabetes (where HDL is low and fasting plasma glucose is poorly controlled) and aerobic conditioning (where HDL is high and fasting plasma glucose is tightly controlled). These findings highlight the possibility that HDL-raising therapies already in advanced clinical development for vascular disease may also have efficacy in the prevention and management of type 2 diabetes.

Drew BG, Duffy SJ, Formosa MF, Natoli AK, Henstridge DC, Penfold SA, Thomas WG, Mukhamedova N, de Courten B, Forbes JM, Yap FY, Kaye DM, van Hall G, Febbraio MA, Kemp BE, Sviridov D, Steinberg GR & Kingwell BA. (2009). High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. *Circulation* **119,** 2103-2111.

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