Diabetes mellitus is a major risk factor for cardiovascular disease, and its prevalence is suspected to further increase in the coming years in the Western hemisphere and also in countries with emerging economies, like India, China, and Brazil. Together with the increasing prevalence of obesity and metabolic syndrome and the subsequent development of arterial hypertension, the epidemic of adiposity and diabetes mellitus may eat up most of the improvement of cardiovascular outcomes that we have seen within the last decades.1

The risk of atherosclerosis is inversely related to circulating levels of high-density lipoprotein (HDL) cholesterol. Results from the Framingham Study demonstrated that this association is independent of low-density lipoprotein. Clinical trials using agents (eg, fibrates) that increase HDL have been shown to decrease cardiovascular event rates. On the other hand, therapy with the HDL-raising substance torcetrapib is associated with increased cardiovascular events, although the mechanism for this remains unclear and is probably independent of the effects on HDL cholesterol.2

The classical function of HDL is the so called “reverse cholesterol transport” removing cholesterol from peripheral tissue and delivering it to the liver by binding of the major HDL apolipoprotein (apo), apoA-I, to the HDL receptor scavenger receptor B type I. Intra-arterial infusion of apoA-I/phosphatidylcholine in hypercholesterolemic patients with normal HDL improves endothelial dysfunction, suggesting that HDL is a positive modulator of vascular NO bioavailability. Infusion of reconstituted HDL even leads to acute changes in human atherosclerotic plaque composition characterized by a reduction in lipid content within the atherosclerotic plaque.3

With respect to endothelial dysfunction in the setting of diabetes mellitus, our group described first an uncoupled endothelial NO synthase (eNOS) in vascular tissue in an animal model of diabetes mellitus.4 With these studies we were able to demonstrate that increased glucose levels cause a protein kinase C-dependent activation of the vascular NADPH oxidase (Figure) leading to the formation of so called “kindling radicals.” These react with NO to form the highly reactive intermediate peroxynitrite (ONOO−), which, in turn, leads to the oxidation of the important eNOS cofactor tetrahydrobiopterin (BH4), to the trihydrobiopterin radical, and to eNOS uncoupling, thereby stimulating the formation of the “bonfire radicals,” which further heat up oxidative stress in vascular tissue.5 Treatment of diabetic animals with the angiotensin II type 1 (AT1) receptor blocker telmisartan improves endothelial dysfunction and, in particular, prevents eNOS uncoupling, pointing to a crucial role of the renin-angiotensin-aldosterone system in mediating this phenomenon.6 In addition to BH4 deficiency because of enhanced ONOO−–mediated BH4 oxidation, a downregulation of the BH4-synthesizing enzyme GTP cyclohydrolase I or the dihydrofolate reductase has been discussed to mediate eNOS uncoupling.

In their article published in the present issue of Hypertension, Van Linthout et al7 describe for the first time a novel function of HDL in 2 models of hyperglycemia. Hyperglycemia lead to a 5-fold increase in the expression of the AT1 receptor in the streptozotocin diabetes model and in cultured endothelial cells. Increased AT1 receptor expression was associated with increased activity and expression of the important superoxide source NADPH oxidase. As shown before,4 eNOS expression in the setting of hyperglycemia in vivo and in vitro was upregulated but dysfunctional (uncoupled), as evidenced by the diminished dimer:monomer ratio established with the Western blotting technique. In diabetic animals, plasma HDL levels were almost doubled by using the technique of adenoviral transfection of apo A-1. Five days after streptozotocin injection, the human Apo A-1 gene transfer was carried out by IV injection of 3×1012 particles per kg containing the E1E3E4-deleted adenoviral vector Ad.hapoA, which induces hepatospecific expression of human apo A-1. This intervention caused a normalization of endothelial dysfunction and a marked reduction in NADPH oxidase activity and expression in vitro and in vivo. The prevention of glucose-induced upregulation of the AT1 receptor by HDL was inhibited in vitro by the eNOS inhibitor Nα-nitro-L-arginine, suggesting indirectly that eNOS was recoupled by HDL. Recoupling of eNOS by HDL treatment was established by the demonstration of a normalization of the dimer:monomer ratio of eNOS protein in aortas.8

Although the authors nicely demonstrate that recoupling of eNOS by HDL is linked to AT1 receptor downregulation and,
therefore, an inhibition of NADPH oxidase activity and expression, several issues remain unresolved.

What is the precise mechanism by which the induction of HDL biosynthesis by transfection of the human apo A-1 gene into diabetic rats ultimately results in a downregulation of AT1R? It can at least be ruled out that the adenovirus carrying the Apo A-1 transgene directly acts on the endothelium, because this is a hepatotropic vector.

What is the contribution of the lysophospholipid constituents of HDL to the beneficial effects of HDL? Sphingosine-1-phosphate and sphingosylphosphorylcholine (see also the Figure) have been shown to exert direct antioxidative and anti-inflammatory effects via inhibition of NADPH oxidase activity and monocyte chemoattractant protein 1 expression via the sphingosine-1-phosphate 3 receptor and scavenger receptor type B1.9 In addition, sphingosine-1-phosphate and sphingosylphosphorylcholine have both been shown to activate eNOS via Akt-mediated phosphorylation of eNOS at 1177serine,10 leading to enhanced NO formation of the enzyme.11 A lysosphingolipid-and/or HDL-mediated downregulation of AT1R has not yet been described in either of these phenomena.

It also remains to be established to what extent the activity and expression of the BH4 synthesizing enzymes, such as GTP cyclohydrolase I and the dihydrofolate reductase, are influenced by HDL treatment.

Taken together, Van Linthout et al7 present a novel feature of HDL, that is downregulation of the AT1R. Ultimately, upregulation by HDL preserves endothelial function in hyperglycemia by preventing eNOS uncoupling. With their article, the authors will encourage researchers to investigate this new and beneficial interaction between HDL and the vasculature in diabetes mellitus and other cardiovascular risk factors, such as hypercholesterolemia and arterial hypertension.

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Disclosures
None.

References


From Menace to Marvel: High-Density Lipoprotein Prevents Endothelial Nitric Oxide Synthase Uncoupling in Diabetes Mellitus by Angiotensin II Type 1 Receptor Downregulation
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