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Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy

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Abstract: **BACKGROUND:** High-density lipoprotein (HDL)-raising therapies are currently under intense evaluation, but the effects of HDL may be highly heterogeneous. We therefore compared the endothelial effects of HDL from healthy subjects and from patients with type 2 diabetes mellitus and low HDL (meeting the criteria for metabolic syndrome), who are frequently considered for HDL-raising therapies. Moreover, in diabetic patients, we examined the impact of extended-release (ER) niacin therapy on the endothelial effects of HDL. **METHODS AND RESULTS:** HDL was isolated from healthy subjects (n=10) and patients with type 2 diabetes (n=33) by sequential ultracentrifugation. Effects of HDL on endothelial nitric oxide and superoxide production were characterized by electron spin resonance spectroscopy analysis. Effects of HDL on endothelium-dependent vasodilation and early endothelial progenitor cell-mediated endothelial repair were examined. Patients with diabetes were randomized to a 3-month therapy with ER niacin (1500 mg/d) or placebo, and endothelial effects of HDL were characterized. HDL from healthy subjects stimulated endothelial nitric oxide production, reduced endothelial oxidant stress, and improved endothelium-dependent vasodilation and early endothelial progenitor cell-mediated endothelial repair. In contrast, these beneficial endothelial effects of HDL were not observed in HDL from diabetic patients, which suggests markedly impaired endothelial-protective properties of HDL. ER niacin therapy improved the capacity of HDL to stimulate endothelial nitric oxide, to reduce superoxide production, and to promote endothelial progenitor cell-mediated endothelial repair. Further measurements suggested increased lipid oxidation of HDL in diabetic patients, and a reduction after ER niacin therapy. **CONCLUSIONS:** HDL from patients with type 2 diabetes mellitus and metabolic syndrome has substantially impaired endothelial-protective effects compared with HDL from healthy subjects. ER niacin therapy not only increases HDL plasma levels but markedly improves endothelial-protective functions of HDL in these patients, which is potentially more important. **CLINICAL TRIAL REGISTRATION:** clinicaltrials.gov. Identifier: NCT00346970.

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Table 1**Characteristics of healthy subjects and diabetic patients**

	Healthy	Diabetics	P -Value
	(n=10)	(n=33)	
Age [years]	65±10	60±11	0.22
Gender [m / f]	8/2	28/5	0.71
BMI [kg/m ²]	27±3	33±4	0.0007
Waist circumference [cm]	91±11	116±13	< 0.0001
MAP [mmHg]	95±8	97±10	0.58
(MetS under antihypertensive therapy)			
Hb_{A1c} [%]	5.4±0.5	6.6±1.0	0.0003
Fasting Glucose [mg/dL]	93±18	128±34	0.009
LDL Cholesterol [mg/dL]	145±26	110±27	0.001
(MetS under statin therapy)			
HDL Cholesterol [mg/dL]	53±22	36±6	0.02
Triglycerides [mg/dL]	168±94	225±213	0.41
HDL Composition:			
Cholesterol [mg/dL]	20.4±6.3	14.9±7.6	0.05
Triglycerides [mg/dL]	2.1±2.9	4.3±3.1	0.07
Protein [mg/dL]	65.5±22.1	57.4±12.2	0.22

BMI, body mass index

Values expressed as mean ± SD

MAP, mean arterial pressure

n.s., not significant

Table 2**Characteristics of diabetic patients before and after placebo or extended-release niacin treatment**

	Placebo (n=15)		ERN (n=15)		P-Value
	Pre	Post	Pre	Post	
Age [years]	62±9		58±11		
Gender [m/f]	12/3		13/2		
BMI [kg/m ²]	34±5		32±4		
MAP [mmHg]	95±9	92±11	99±8	93±9	0.37
HbA1c [%]	7.1±1.0	6.9±1.0	6.3±0.9	6.5±0.8	0.18
Fasting Glucose [mg/dL]	134±38	130±28	123±31	127±31	0.32
LDL-Cholesterol [mg/dL]	112±31	101±29	107±24	101±28	0.96
HDL-Cholesterol [mg/dL]	35±7	33±5	36±6	42±5	0.001
Triglycerides [mg/dL]	290±284	297±232	160±62	118±61	0.06
<i>HDL Composition:</i>					
Cholesterol [mg/dL]	12.2±3.5	12.1±3.7	17.5±8.9	14.4±4.5	0.28
Triglycerides [mg/dL]	4.5±3.2	3.8±2.9	4.0±2.6	2.2±1.7	0.11
Protein [mg/dL]	55.9±8.9	59.2±11.8	55.8±12.3	58.7±14.1	0.82
<i>Medication</i>					
ACE/ARB	10/15		09/15		
ASS	12/15		10/15		
Diuretic	05/15		03/15		
Calcium-Antagonist	04/15		02/15		
Beta-Blocker	13/15		10/15		
Statin	15/15		15/15		
Oral Antidiabetic Drug	4/15		05/15		
Insulin	3/15		02/15		

Values are expressed as mean ± SD

The P-values relate to the statistical analyses of changes (i.e. treatment effects) of the ERN vs. the Placebo group.