Reconstituted HDL Increases Circulating Endothelial Progenitor Cells in Patients With Type 2 Diabetes

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Recent articles in this journal suggest a new role for HDL in endothelial progenitor cell (EPC)-mediated endothelial repair. We investigated the effect of increasing HDL levels by systemic infusion of reconstituted HDL (rHDL) on EPC availability in patients with type 2 diabetes (DM2). Patients with DM2 have reduced availability and impaired function of EPCs, indicative of impaired vascular repair. Patients with DM2 have reduced availability and impaired function of EPCs, indicative of impaired vascular repair. Our data show for the first time that a beneficial effect of increasing HDL levels on EPC biology also occurs in humans.

Seven patients with uncomplicated DM2 (age 53.6 ± 3.0 years; 3 females/4 males; glycylated hemoglobin A1c 7.1 ± 0.3%) were included in the study. The institutional review board approved the study, and all subjects gave written informed consent. Patients used only metformin. They had mild dyslipidemia (total cholesterol 5.6 ± 0.4 mmol/L; LDL cholesterol 2.9 ± 0.6 mmol/L; HDL cholesterol 1.1 ± 0.2 mmol/L; triglycerides 1.5 ± 0.4 mmol/L). Patients received systemic rHDL infusion (80 mg/kg body weight for 4 hours, CSL-111, CSL Behring AG). rHDL consists of apolipoprotein A-I (apoA-I) isolated from human plasma and phosphatidylcholine (PC) from soy bean. ApoA-I and PC are combined in a molar ratio of 1:150, and form disc-shaped noncovalently-associated particles resembling nascent HDL.

Patients’ blood samples were drawn before (baseline), directly (t = 7) after, 24 hours (t = 24) after, and 7 days (t = 7d) after rHDL-infusion. ApoA-I plasma levels were measured by rate nephelometry. Circulating EPCs, defined as CD34+/VEGFR-2+ cells, and hematopoietic CD34+ cells were determined in peripheral blood by flow cytometry. Data are presented as mean ± SEM, and comparisons between groups were made by 1-way ANOVA for repeated measurements. A probability value < 0.05 was considered significant.

After rHDL-infusion plasma apoA-I increased from 1.2 ± 0.2 (baseline) to 2.8 ± 0.6 g/L (t = 7, P < 0.001), and returned to baseline level at t = 7d (1.5 ± 0.3 g/L; n.s. compared with baseline). Interestingly, 1 week after rHDL infusion we observed a marked increase in the number of EPCs (Figure; baseline 480 ± 85 versus t = 7d 1060 ± 347 mL blood, P < 0.05), indicating a late effect of rHDL infusion on EPC availability. The number of CD34+ cells was measured at baseline 3200 ± 632, t = 7d 3395 ± 688, t = 24h 3396 ± 777 mL blood, and was significantly increased at t = 7d 4694 ± 670 mL blood versus baseline (P < 0.001).

The late increase in EPCs after rHDL infusion can be explained by several mechanisms. rHDL may enhance EPC mobilization by a beneficial effect on NO bioavailability in the BM. Consistently, rHDL administration in eNOS−/− mice had no effect on blood flow recovery. However, we observed no differences in plasma levels of VEGF165, one of the principal mobilizers of EPCs from BM, between the different time points. Another possible mechanism is that rHDL enhances the number of EPCs by increasing their survival through prevention of apoptosis by inhibiting caspase-3 activity. The exact effect of HDL on EPC kinetics hence remains to be elucidated.

We cannot fully exclude an effect of PC on EPC number after rHDL infusion; PC-only infusion resulted in hemoysis in rabbits and can therefore not be tested. Furthermore, it is unlikely that cholate contributes to a rise in EPCs one week later as it mainly pertains to mobilizing cholesterol predominantly from the liver into the bile and is excreted rapidly.

In conclusion, our findings together with two other recent reports point toward a novel role for HDL particles in EPC-mediated repair. We demonstrate for the first time that an increase in HDL levels can improve EPC availability in patients with DM2, lending further support to HDL-increasing strategies also in acute settings.
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Disclosures
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