Carbamylation Impairs the Functional Integrity of High-Density Lipoprotein (HDL)

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In inflammatory diseases like atherosclerosis and renal disease, HDL can lose its atheroprotective characteristics. Dysfunctional HDL particles can impede reverse cholesterol transport, enhance oxidation of LDL, and increase vascular inflammation. Renal disease is associated with increased modification of proteins at sites of pathology. Recently it has been demonstrated that serum levels of carbamylated proteins are an independent predictor of mortality risk among hemodialysis patients. Furthermore, it was recently shown that the extent of HDL- modification correlates with the poor outcome in hemodialysis patients

Herein, we report that HDL associated apoA-I is carbamylated in plasma and aortic lesions of patients suffering from renal disease. Immunohistochemical studies confirmed co-localization of carbamylated epitopes with apoA-I and macrophages in human atherosclerotic lesions. To identify specific carbamylation sites of apoA-I, we performed shotgun proteomic analysis of HDL isolated from control and hemodialysis-patients. We could identify 9 out of 22 apoA-I associated lysine residues that are specifically carbamylated. Interestingly, all carbamylated lysine residues are located in the α-helical lipid binding domains of apoA-I, indicating that carbamylation of apoA-I affect the functional integrity of HDL. In line with that observation, we observed that *in vitro* carbamylated HDL (i) leads to "nonproductive" binding to the HDL receptor (SR-BI), (ii) decreased SR-BI mediated cholesterol efflux, (iii) reduced paraoxonase (PON) activity.

Taken together, our data provide strong evidence that carbamylation renders HDL dysfunctional.