Modification of HDL by γ-Ketoaldehydes Causes impaired HDL Function in Familial Hypercholesterolemia

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Background: Dysfunctional high density lipoprotein (HDL) is linked to the pathogenesis of atherosclerosis and cardiovascular events. Lipid peroxidation products have been reported to enhance atherogenesis and compromise HDL atheroprotective functions. The role of γ-ketoaldehyde modification on HDL function and atherosclerosis was examined in the setting of familial hypercholesterolemia (FH) and by using *Ldlr*$^{-/-}$ mice as an atherosclerotic model. **Methods and Results**: Sandwich enzyme-linked immunosorbent assay (ELISA) of HDL malondialdehyde (MDA) content revealed that HDL from subects with FH contained 5.7-fold ($P<0.01$) more MDA compared to control HDL. Analysis by Western blot demonstrated that FH HDL contained 5.9- and 3.6-fold ($P<0.01$) more MDA-apoAI and isolevuglandins (isoLGs)-apoAI adducts compared to control HDL, respectively. Heterozygous (het)-FH versus control HDL was 42% ($P<0.01$) less efficient at reducing cholesterol stores in apoE$^{-/-}$ foam cells. In the presence of LPS, het-FH HDL stimulated 2.9- and 3.3-fold ($P<0.05$) more expression of IL-1β and TNF-α in apoE$^{-/-}$ cells versus control HDL, suggesting impaired anti-inflammatory function. Importantly, IsoLG modification of apoAI decreased the cholesterol efflux capacity by 71% ($P<0.01$). HDL from *Ldlr*$^{-/-}$ mice fed a Western versus a chow diet contained 6.2-fold ($P<0.01$) more MDA-apoAI and stimulated 57% ($P<0.05$) and 71% ($P<0.01$) more expression of inflammatory IL-1β and TNF-α. Administration of the ketoaldehyde scavenger, salicylamine (SAM), versus the nonreactive analogue, 4-SAM, to *Ldlr*$^{-/-}$ mice consuming a Western diet reduced the HDL MDA-apoAI content by 55.8% ($P<0.01$). Importantly, 3 months of SAM treatment reduced atherosclerosis of *Ldlr*$^{-/-}$female mice fed a Western diet for 16 weeks by 42% ($P<0.01$) as analyzed by Oil-Red-O staining of proximal aortic sections. **Conclusions**: Our studies suggest that FH HDL function is impaired as a result of increased MDA and isoLG modification and identify ketoaldehyde scavenging as a potential therapeutic means to prevent atherosclerosis development.

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