Dyslipidemia alters HDL metabolism and function in NAFLD

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Dyslipidemia and inflammation play key roles in the pathogenesis of both nonalcoholic fatty liver disease (NAFLD) and atherosclerosis. NAFLD, particularly its severe form non-alcoholic steatohepatitis (NASH) is associated with increased cardiovascular disease (CVD) risk. HDL (a CVD risk) are decreased in NAFLD but whether HDL function is abnormal in NAFLD is unknown. The aim of this study was to investigate HDL function and to examine the effect of dyslipidemia and inflammation on HDL metabolism in patients with biopsy proven simple steatosis (SS) and NASH. H_2O-metabolic labeling was used to study HDL function and HDL protein dynamics in SS, NASH patients (8/group) and matched healthy controls (n=9) in vivo. To assess the role of HDL maturation and remodeling on stability of HDL proteins, we quantified the activities of cholesterol ester transfer protein (CETP), the key HDL protein involved in HDL lipidation. HDL's anti-oxidant, anti-inflammatory and cholesterol efflux properties were measured using in vitro assays. Compared to controls, SS and NASH subjects had significantly higher levels of plasma triglyceride, insulin, and were more insulin resistant (HOMA, $P<0.05$) with no differences in total cholesterol, HDL cholesterol (HDLc), ApoB100 and ApoAI levels. NAFLD patients had increased production and degradation rates of both HDLc and ApoAI that kept their levels stable. The degradation rates also were increased of other HDL proteins. NAFLD patients had increased activities of CETP, indicating altered HDL lipidation. NAFLD induced alterations in HDL metabolism were associated with reduced anti-oxidant but increased pro-inflammatory activity of HDL ($P<0.05$)). However, no differences were observed in either HDL function or the kinetics of HDLc and HDL proteins between SS and NASH subjects. HDL turnover and function are altered in NAFLD without any differences between SS and NASH, indicating that dyslipidemia is more important than hepatic inflammation on altered HDL metabolism and functions in NAFLD.

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