Poster 047

LECTIN-LIKE OXIDIZED LDL RECEPTOR-1 (LOX-1) POLYMORPHISM IS INDEPENDENTLY ASSOCIATED WITH LIVER HISTOLOGY IN NON-ALCOHOLIC-STEATO-HEPATITIS (NASH)

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Background. Nonalcoholic steatohepatitis (NASH) encompasses a histological spectrum ranging from simple steatosis to steatosis plus necroinflammation. It affects 3-5% of general adult population. NASH is associated with an increased risk of developing cirrhosis/end-stage liver disease, diabetes and cardiovascular disease (CVD); the correlation of liver histology in NAFLD with the severity of early atherosclerosis and with the impairment in glucose metabolism suggests the same molecular mechanisms may underlie liver injury, diabetes and atherogenesis. The knowledge of such mechanism(s) would help select NASH subjects at greater risk of cardio-metabolic and liver-related complications for early specific interventions and tight monitoring. Lectin-like oxidized LDL receptor-1 (LOX-1) has been connected to cardiovascular risk in the general population and to insulin resistance in experimental models. Several LOX-1 functional single nucleotide polymorphisms (SNPs) have been recently linked to CVD susceptibility in humans. The IVS4-14 A>G SNP is one of these functional SNPs.
Objective. To assess the impact of the common functional IVS4-14 A>G LOX-1 polymorphism on liver disease, cytokines, lipoprotein metabolism and glucose homeostasis in NASH.
Methods. Forty nonobese, nondiabetic, normolipidemic biopsy-proven NASH patients and 40 age, sex, BMI and IVS4-14 A>G LOX-1 polymorphism-matched healthy controls underwent an oral fat load test (OFT), with measurement of plasma triglyceride-rich lipoprotein subfractions, oxidized LDL, total antioxidant status (TAS), adipokines, and cytokeratin-18 fragments (marker of hepatocyte apoptosis). Subjects underwent also an oral glucose tolerance test (OGTT), with Minimal Model analysis to yield parameters of glucose homeostasis.
Results. LOX-1 polymorphism was independently associated with liver histology (with G allele carriers having a more severe liver disease); during the OFT, the G allele was associated with small triglyceride-rich lipoprotein accumulation, lower TAS levels, adipokine imbalance (higher resistin and lower adiponectin) and increased cytokeratin-18 fragments.
Conclusions. We provided evidence that the LOX-1 IVS4-14 A>G SNP was independently associated with the severity of liver disease in NASH, even after adjustment for adipokines and other confounders, suggesting LOX-1 function may directly modulate liver disease progression in NASH. LOX-1 IVS4-14 A>G SNP may be the connection among liver injury, diabetes and CVD in NASH. Further in vitro and adequately-powered prospective studies need to elucidate underlying mechanisms and to assess the usefulness of LOX-1 IVS4-14 A>G SNP for screening and treatment of patients at higher liver-related, metabolic and cardiovascular risk.