Resmetirom protects against diet-induced MASLD and reduces atherogenic risk factors in obese Ldlr-/--Leiden mice

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Background and Aims: The thyroid hormone receptor-β agonist MGL-3196 (Resmetirom) is expected to become the first approved drug for metabolic dysfunction-associated steatotic liver disease (MASLD). Since resmetirom was found to lower plasma LDL cholesterol levels in clinical trials, it may also affect obesity-associated cardiovascular disease (CVD), which is the primary cause of mortality in MASLD patients. The Ldlr-/--Leiden mice have previously been compared with biopsy-confirmed MASLD patients, which demonstrated that patients with a high risk of developing CVD are particularly well reflected by the Ldlr-/--Leiden mouse model. In the present study we studied the effect of resmetirom on progression of atherosclerotic CVD, in addition to its effects on MASLD-associated liver fibrosis.

Method: Ldlr-/--Leiden mice underwent an initial 18-week period of fast-food diet (FFD) feeding to establish early stages of MASLD and atherosclerosis. After this run-in period, one group of mice was terminated as a start-of-treatment reference. The remaining mice were maintained on FFD and received vehicle (FFD + vehicle controls) or 3 mg/kg resmetirom (FFD + Res) by oral gavage for an additional 10 weeks after which they were terminated at t=28 weeks. Chow-fed mice were included as a healthy reference group. Plasma parameters, liver, adipose and heart tissues, were analyzed in the study.

Results: FFD fed mice developed obesity, dyslipidemia as confirmed by elevated plasma cholesterol and triglycerides levels, and MASLD associated liver fibrosis as compared to chow-fed controls. Therapeutic treatment with resmetirom significantly reduced plasma cholesterol and triglycerides compared to FFD + vehicle-treated controls. Plasma lipoprotein profiles demonstrated that the FFD-induced increase in plasma TGs can mainly be ascribed to an increase in VLDL lipoprotein particles and the increase in plasma cholesterol to an increase in (V)LDL-sized particles. Resmetirom lowered atherogenic risk factors, i.e. TG in VLDL and cholesterol in (V)LDL-sized particles. Subsequent effects on atherosclerosis will be presented (analysis ongoing). Notably, all effects were observed independent of changes in body weight, adiposity, and food intake, as resmetirom did not impact these factors. Furthermore, FFD-induced circulating liver injury markers ALT and AST were significantly reduced upon resmetirom treatment, and reduced to that in the chow-fed group. Consistent with this data, MASLD-associated liver fibrosis was attenuated with resmetirom relative to the FFD control group, as hepatic collagen content corrected for total liver weight was significantly reduced with resmetirom.

Conclusion: Our findings demonstrate that in Ldlr-/--Leiden mice, treatment with resmetirom has additional protective effects on CVD risk factors and possibly on the extent of atherosclerosis, on top of its effects on MASLD.