Obeticholic acid attenuates fibrosis development in a high fat diet induced NASH model (LDLr-/-.Leiden mice)

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The LDLr-/-.Leiden mouse is a translational, diet-inducible model for non-alcoholic steatohepatitis (NASH) with associated fibrosis, displaying many clinically relevant features of NASH. Here, we aimed to study whether the progression of fibrosis in this model can be retarded or reverted by dietary or pharmaceutical intervention. To this end, we fed LDLr-/-.Leiden mice a high-fat diet (HFD) for 24w, after which mice were randomized into 4 groups: one group was sacrificed, one continued on HFD, one was switched to chow (dietary intervention) and one received HFD + 10 mg/kg obeticholic acid (OCA) for the remainder of the study (up to 34w). Development of NASH and hepatic fibrosis was assessed blindly by a pathologist, as well as by direct measuring collagen synthesis rates (assessed as the incorporation of deuterium from heavy water into the stable C-H bonds of hydroxyproline (OHP) in the newlysynthesized protein). Both interventions improved hepatic steatosis and inflammation, which were manifest after 24w and continued to progress in the 34w HFD group. After 24 weeks of HFD feeding, mice displayed mild fibrosis (5.6±1.4% of perisinusoidal area) which progressed to 25.3±4.9% after 34w of HFD. Mice that were switched to chow diet or treated with OCA showed reduced fibrosis development (9.8±2.8% and 14.5±3.4% at t=34w resp., both $p<0.05$ vs HFD at t=34w). In line with this, analysis of de novo collagen synthesis showed that both the dietary and the OCA intervention reduced the rate of fibrogenesis relative to HFD control (10.8±1.0% new OHP in 14 days in HFD; 7.5±1.0% in chow and 8.3±0.6% in OCA; both $p<0.05$ vs HFD). Together these data show that LDLr-/-.Leiden mice develop NASH with progressive fibrosis when fed a HFD, which is modifiable by dietary and pharmaceutical interventions.