Statin treatment upregulates intestinal lipid secretion pathways in a rodent model of insulin resistant and CVD, the JCR:LA-cp rat.

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Purpose of Study: Statins are widely used for the treatment of hyperlipidemia to reduce the risk of cardiovascular disease (CVD). Intriguingly, recent reports suggest that whilst Statins are effective in reducing hepatic cholesterol synthesis, they in turn may upregulate intestinal cholesterol synthesis. The direct effects and/or mechanisms of this phenomenon remain largely unknown.

Methods and Results: Obese and insulin resistant (IR) JCR:LA-cp rats received a 1% cholesterol diet containing Simvastatin (0.01% w/w), for 8 weeks. Fasting and postprandial plasma biochemical profile was assessed using enzymatic assays and a modified apoB48 (chylomicron; CM) western blotting protocol. Statin treatment reduced fasting plasma TG (-64%), cholesterol (-24%) and postprandial plasma apoB48 (-58%). Ussing Chamber techniques assessed intestinal net cholesterol influx (absorption) and net cholesterol efflux (TICE); Statin treatment did not exert any effect on either intestinal cholesterol absorption or TICE in IR JCR:LA-cp rats versus control. The expression of intestinal lipogenic genes were assessed by quantitative real-time PCR. Statin treatment increased (1-2 fold) mRNA levels of Npc1l1, Abcg5/g8, Hmgcr and Srebp2, in the intestine of IR versus non-IR rats. The intestinal secretion of lipids into mesenteric lymph was assessed by mesenteric lymph duct cannulations. Interestingly, compared to control, IR rats treated with Statin secreted greater cholesterol (2.1-fold) and TG (1.5-fold) into mesenteric lymph.

Conclusions: In an obese rodent model of IR, Statin treatment adversely upregulates intestinal lipid secretion and lipogenic gene expression and may confound benefits to remnant dyslipidemia.