# High fat induced insulin resistance: the emerging role of hepatokines

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**Introduction:**
A link between serum hepatokine levels (proteins produced by the liver and acting distantly) and insulin resistance in type 2 diabetes has been recently suggested. Here, we wanted to explore the liver expression of several hepatokines at the initiation of a high fat diet in mice, as well as their relation with liver macrophage (Kupffer cell) activation.

**Material and methods:**
Male mice of 5 weeks of age were fed a normal diet (ND) or a high fat diet (HFD) for 3 days, known to induce steatosis and insulin resistance. A preventive Kupffer cell (KC) depletion was obtained by intravenous injection of clodronate loaded liposomes and compared with PBS liposomes. The mRNA expression of hepatokines (selenoprotein-P, fetuin-A, fibroblast growth factor 21, angiopoietin-like protein 3) was evaluated by RT-PCR on liver tissue.

**Results:**
Short term HFD induced steatosis, KC activation and insulin resistance with a significant increased expression of selenoprotein P (1.6 fold, $p<0.001$), fetuin-A (1.7 fold, $p<0.01$) and fibroblast growth factor 21 (9 fold, $p<0.01$). However, the liver expression of angiopoietin-like protein 3 remains unchanged under short term HFD. Kupffer cell depletion in this setting did not reduce hepatic steatosis but significantly ameliorated insulin sensitivity proved by clamp studies. This amelioration in insulin sensitivity in KC-depleted mice was associated with a significant decrease in fetuin A mRNA expression (0.7 fold, $p<0.001$) compared to animals with KC. Interestingly, while selectively depleting liver macrophages without affecting adipose tissue macrophage infiltration, intravenous clodronate injection was associated with a significant reduction in epididymal adipose tissue expansion compared to PBS injection (1.1% of body weight versus 1.6% of body weight, $p<0.001$), suggesting a role of liver-derived products in peripheral tissue alterations associated with obesity.

**Conclusions:**
We demonstrate liver hepatokine overexpression at the initiation of HFD feeding, concurrent with hepatic steatosis and insulin resistance. Targeting KC in this setting improved insulin sensitivity and was associated with a decreased adiposity and a reduced liver fetuin A expression. The impact of this hepatokine on adipose tissue metabolism needs to be confirmed and the search for pathogenic liver-derived factors in obesity associated disorders intensified.