# Effects of Diet, Gender, and Age on Liver Metabolism Upon Feeding a High Fat Diet

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**Background/Objective:** Currently, 30% of the USA population has non-alcoholic fatty liver disease (NAFLD), a condition that is increasing in parallel with the global obesity epidemic and life expectancy and is a risk factor for type 2 diabetes and cardiovascular disease. Aberrant transcriptional control of genes is a hallmark of metabolic disease. Thus, it is of interest to characterize how diet, age, and sex impacts various metabolic and signaling pathways upon progression to NAFLD.

**Methods:** A cohort of 7-week or 52-week-old male and female mice (n=8) were assigned a high-fat diet (HFD) or a low-fat diet (LFD) feeding regimen for 10 weeks, after which serum chemistries were obtained. Subsequently, gene expression in hepatic tissue samples was analyzed using RNA-seq and Western Blot.

**Results:** In both males and females, HDL, LDL, and total cholesterol were significantly increased with HFD in both age groups. In females, there was no significant difference in fasting blood glucose and insulin levels between any groups, while in males, both markers were significantly increased with HFD. RNA-seq data showed significant changes in gene expression correlating with diet, gender, and age. KEGG pathway analysis showed clustering of genes in fatty acid oxidation and synthesis pathways in mice fed a HFD, without affecting cholesterol synthesis enzymes. In aged mice, genes involved in extracellular matrix-receptor interaction were among the most affected. In males and females, young and aged, Western Blot analysis showed decreased expression of lipogenic enzymes ATP-citrate lyase and fatty acid synthase with HFD, but no changes of enzymes of cholesterol synthesis, confirming the RNA-seq data. No significant alterations were observed in insulin signaling.

**Conclusion and Potential Impact:** A HFD leads to a more severe phenotype in males than females, including increased fasting and non-fating glucose as well as insulin, and age exacerbates these abnormalities. Cholesterol is increased in both genders and is also exacerbated by age.