A Chronic High Fructose Diet Induces Progressive Murine NASH with Early Mitochondrial Aging

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Background
Non-alcoholic fatty liver disease (NAFLD) and the more serious sub-category non-alcoholic steatohepatitis (NASH), have quickly become recognized as one of the most common causes of liver disease in both adults and children in the world. Diets high in saturated fat and fructose are factors leading to obesity and NASH in humans. Case reports demonstrate mitochondria ultra-structural changes obtained from humans with histological NASH with progressing development to uncover mechanisms in development of NASH, diagnostic tools to differentiate the severity and progression of the disease, and ultimately treatment options.

Hypothesis/Aims
The objective is to outline the progression of ultra-structural changes in mice on a NASH-inducing diet, corroborate the findings through mtDNA quantification, and investigate interplay endoplasmic reticulum stress markers.

Methods
C57Bl/6 mice were randomized to a Chow (C) or high-fat, high-fructose (HF2) diet for 8, 16, or 32 weeks until time of sacrifice. Body weights were monitored until time of sacrifice at which time liver was collected to evaluate electron microscopy (EM), DNA content and gene expression by RNAseq and RT-PCR were evaluated.

Results
HF2 mice gained more weight, had higher plasma ALT levels and hepatic triglycerides at all time points. HF2 mice mitochondria first became smaller and then larger than their C fed counterparts. On the other hand mitochondrial DNA content decreased over time. ER Stress markers, PERK and CHOP, were significantly increased with our HF2 diet.

Conclusions
Our NASH-inducing diet in mice led to progressive decrease in DNA content, supporting a role for mitochondria in the development of NAFLD and NASH. This finding did not directly correlate with mitochondrial size and number. In our model we observed an early decrease in mitochondria size similar to that seen with normal aging. This disconnect may be secondary to small sample size and follow-up studies employing more subjects is warranted. Additional evaluation through metabolic studies to suggest a specific biochemical dysfunction would be beneficial as well.

Acknowledgements
This study was supported in part by USPHS grants T32 DK07727 and NIH grant T35 DK 60444.