Effect of dietary intervention on hepatocellular senescence and mitochondrial dysfunction in the GAN diet-induced obese mouse model of NASH

Authors: Malte Hasle Nielsen, Denise Oro, Morten Lundth, Martin Rann Madsen, Jens Christian Nielsen, Mathias Flenssted-Jensen, Cecile Holngaard Andersen, Steen Larsen, Michael Feigh

Corresponding author: Michael Feigh · mfe@Gubra.dk · Gubra Aps · Hørsholm, Denmark

Background & Aim

The prevalence of obesity-associated non-alcoholic steatohepatitis (NASH), with development of hepatic fibrosis, increases with age. This study aimed to evaluate dietary intervention on disease progression, hepatocellular mitochondrial respiratory capacity, and transcriptome profile in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of NASH.

Study outline

- Improvement in metabolic and histological parameters
- Histopathological NAFLD Activity Score and Fibrosis Stage
- Improved hepatocellular mitochondrial respiratory capacity
- Transcriptomic profile for hepatocellular senescence

**Figure 1.** Chow reversal improves metabolic and histological parameters in DIO-NASH mice. (A) Body weight (g). (B) Hepatocytes with lipid droplets (%). (C) Inflammatory factor (X s). (D) Liver collagen type III (%). (E) Livers of mice with NASH. (F) Liver collagen type III (%). (G) Liver weight (g ± SEM). (H) Liver weight (g ± SEM). Chow reversal compared to corresponding DIO-NASH-vehicle group (Bonferroni test and/or linear model).

**Figure 2.** Chow reversal improves histopathological scores in DIO-NASH mice. Histopathological scores were determined by a blinded histopathologist using the NAFLD fibrosis score (NAS) method. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage (F). (C) Comparison of individual pretreatment NAS. (D) Comparison of individual post-treatment NAS. Chow reversal compared to corresponding DIO-NASH-vehicle group (Bonferroni test and/or linear model).

**Figure 3.** Chow reversal improves hepatocellular mitochondrial respiratory capacity in DIO-NASH mice. High-resolution respiratory assessment of MRC Complex I, Complex II, Complex + III + IV, and Complex + III + IV + V respiratory capacity following 10 weeks of chow reversal. **P < 0.05, ***P < 0.001 compared to DIO-NASH vehicle group (Bonferroni test and/or linear model).

**Figure 4.** Chow reversal suppresses hepatocellular senescence-associated transcriptomic signatures in aged DIO-NASH mice. Aged mice are compared to DIO-NASH-vehicle group (Bonferroni test and or linear model).