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

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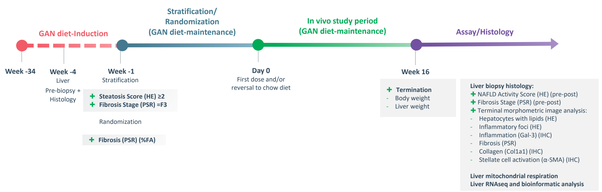
Background & Aim

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



No. #	Animal model	Group name	Number of animals	Dose [mg/kg]	Dosing Frequency	Route of administration
1	LEAN-CHOW	Chow (vehicle)	10	-	QD	PO
2	DIO-NASH	Vehicle	16	-	QD	PO
3	DIO-NASH	Chow reversal (vehicle)	16	-	QD	PO

Improvement in metabolic and histological parameters

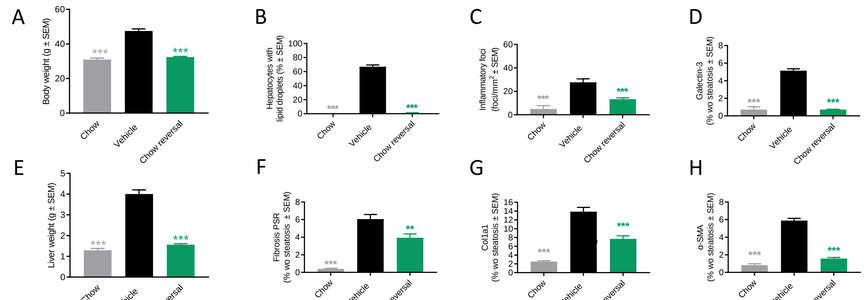


Figure 1. Chow reversal improves metabolic and histological parameters in DIO-NASH mice. **(A)** Terminal body weight (g). **(B)** Hepatocytes with lipid droplets (%). **(C)** Inflammatory foci/mm2 (%). **(D)** Liver galectin-3 (%). **(E)** Terminal liver weight (g). **(F)** Liver fibrosis PSR (%). **(G)** Liver Collagen 1a1 (%). **(H)** Liver α-SMA. **p<0.01, ***p<0.001 compared to corresponding DIO-NASH vehicle group (Dunnett's test one-factor linear model).

Histopathological NAFLD Activity Score and Fibrosis Stage

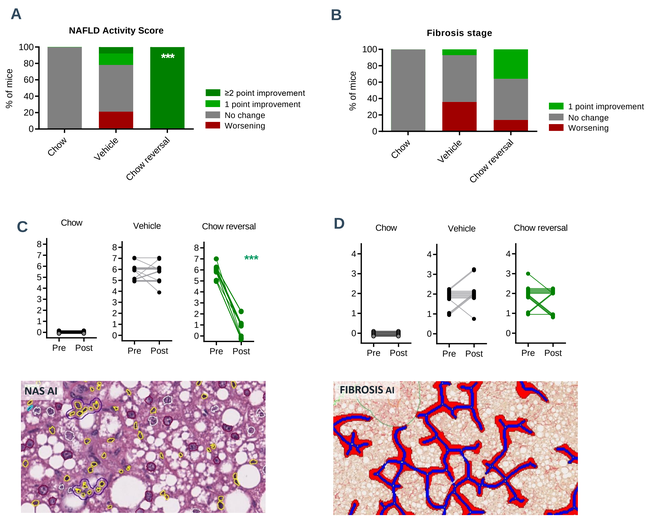


Figure 2. Chow reversal improves histopathological scores in DIO-NASH mice.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C)** Comparison of individual pre-post NAS. **(D)** Comparison of individual pre-post Fibrosis stage. ***p<0.001 to corresponding DIO-NASH vehicle group (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: Representative HE and PSR photomicrographs from DIO-NASH animal used for GHOST evaluation.

Improved hepatocellular mitochondrial respiratory capacity

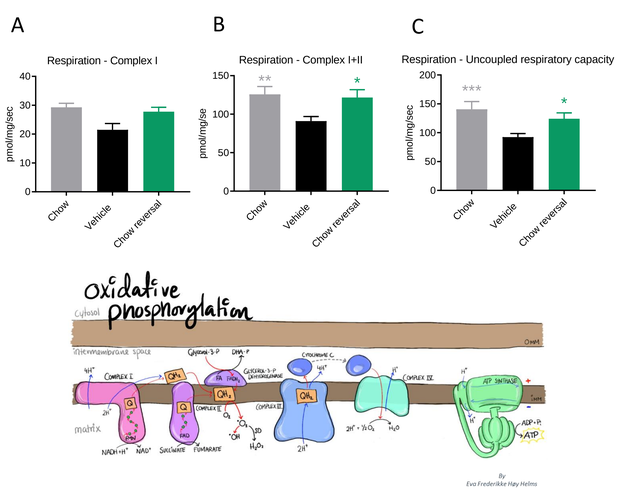


Figure 3. Chow reversal improves hepatocellular mitochondrial respiratory capacity in DIO-NASH mice.
High-resolution respirometry assessment of **(A)** Complex I, **(B)** Complex I + II, and **(C)** uncoupled respiratory capacity following 16 weeks of chow reversal. **p<0.01, ***p<0.001 compared to DIO-NASH vehicle group (Dunnett's test one-factor linear model).

Transcriptomic profile for hepatocellular senescence

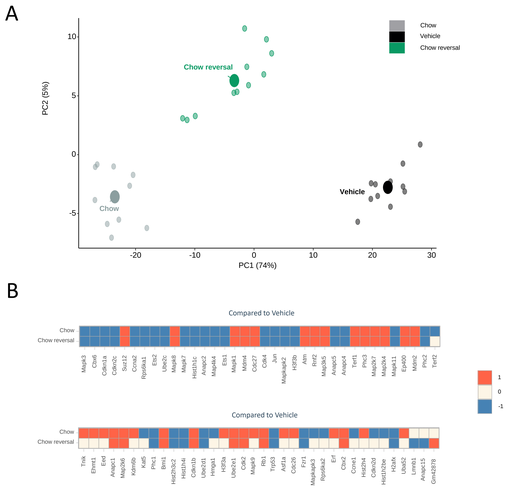


Figure 4. Chow reversal suppress hepatocellular senescence-associated genes in DIO-NASH mice.
(A) Principal component analysis of the 500 most variable genes. **(B)** Heatmap of senescence-associated genes derived from the Reactome Pathway "Cellular Senescence". Blue and red colour gradients indicate the log2FC of significantly (p<0.05) down- and up-regulated gene expression, respectively. White boxes indicate genes not significantly (p>0.05) regulated.

CONCLUSION

- Dietary intervention normalized body weight and liver weight in aged DIO-NASH mice.
- Dietary intervention reduced histological markers for steatosis, inflammation and fibrosis in aged DIO-NASH mice.
- Dietary intervention improved NAFLD Activity Score and Fibrosis Stage in aged DIO-NASH mice.
- Dietary intervention improved hepatocellular mitochondrial respiratory capacity in aged DIO-NASH mice.
- Dietary intervention improved hepatocellular senescence-associated transcriptomic signatures in aged DIO-NASH mice.
- The aged GAN DIO-NASH mouse model is suitable for profiling novel drug therapies for hepatocellular senescence and mitochondrial respiratory capacity.