Metabolic, biochemical, histopathological, and transcriptomic effects of dietary intervention in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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Background & Aim

Current standard of care for NASH involves lifestyle modification, notably dietary intervention, aiming to promote regression or resolution of non-alcoholic steatohepatitis (NASH) and liver fibrosis. The present study aims to evaluate the metabolic, biochemical, histopathological, and transcriptomic effects of dietary intervention (chow-reversal) in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH.

Study outline

- DIO-NASH
- Vehicle + chow-reversal
- Pre Post
- Weight, plasma ALT and liver lipids.
- Liver histology, extracellular fibrosis, hepatic steatosis.

Improvement in metabolic and biochemical parameters

- Significant improvement in metabolic and biochemical parameters.
- Comparative transcriptomic analysis.
- Associated changes in liver histology.

Improvement in NAFLD Activity Score and Fibrosis Stage

- Significant improvement in NAFLD Activity Score.
- Fibrosis stage significantly reduced.

Improvement in quantitative histology of steatosis, inflammation and fibrosis

- Steatosis, inflammation, and fibrosis significantly reduced.
- Comparative histology.

Improvement in transcriptomic profile for fibrosis

- Associated changes in liver histology.
- Comparative transcriptome.

Figure 3 - Chow-reversal improves liver histopathological scores in GAN DIO-NASH mice

Histopathological scores were determined by Gubra histopathological Objective Scoring Technique (HOS) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Liver stage. (C) Comparison of individual pre-post NAS, and individual pre-post NAS change. ***p<0.001 compared to corresponding GAN DIO vehicle control (Kruskal-Wallis test, Dunn’s test as factor linear model).

Figure 3 - Chow-reversal improves liver histological markers in GAN DIO-NASH mice

Histological/morphometric assessments were performed by GAN HOS deep learning-based image analysis on scoring-associated variables (panels A-E) on conventional HE or immunohistochemistry (panels F-H) with histopathological interpretation.

CONCLUSION

- Chow-reversal normalizes body weight, plasma ALT and liver lipids.
- Chow-reversal promotes p2-point significant improvement in NAFLD Activity Score.
- Fibrosis stage was unaffected by chow-reversal, illustrating highly stable collagen architecture.
- Chow-reversal reduces quantitative histological markers of steatosis, inflammation and fibrosis.
- Chow-reversal demonstrates transcriptomic suppression of fibrosis-associated gene expression.
- These findings agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model.