Optimizing Key Dietary Nutrients to Accelerate Induction of a Next-Generation MASH Animal Model

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Introduction

The global incidence of metabolic dysfunction-associated steatohepatitis (MASH) is increasing, presenting a significant public health challenge. The pathogenesis of MASH reflects a complex interplay of metabolic disorders, inflammation, and oxidative stress [1]. Diet-induced rodent models remain the most widely used preclinical approaches for studying MASH progression and therapeutic efficacy [2]. Among these, Gubra-Amylin NASH (GAN) diet is a well-recognized high-fat, high-fructose, and high-cholesterol dietary model that recapitulates several key features of human MASH [3]. However, GAN diet-induced MASH mouse model requires at least 32 weeks of induction with mild fibrosis. Other currently available models either require prolonged feeding periods or incompletely replicate the liver pathology and associated co-morbidities observed in patients. Thus, there is a critical need for new models that can rapidly and precisely simulate (or reproduce) the pathological features of human MASH.

Objective

This study aims to develop novel models by fine-tuning key dietary compositions to rapidly reproduce human MASH features and efficacy of key test compounds.

Methods

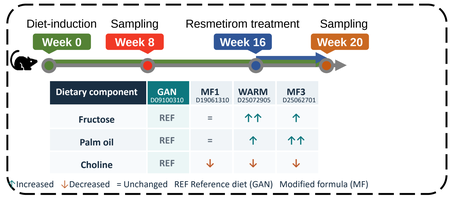

Fig. 1 Establishment of the MASH model via optimized diet formulas. Male C57BL/6J mice were randomized into six groups to receive three modified diets, a standard GAN, chow, or a purified diet control (D16120211, PLF), respectively. Resmetirom treatment was initiated at Week 16, and mice were sacrificed at Weeks 8 and 20 to jointly characterize model development and therapeutic efficacy.

Results

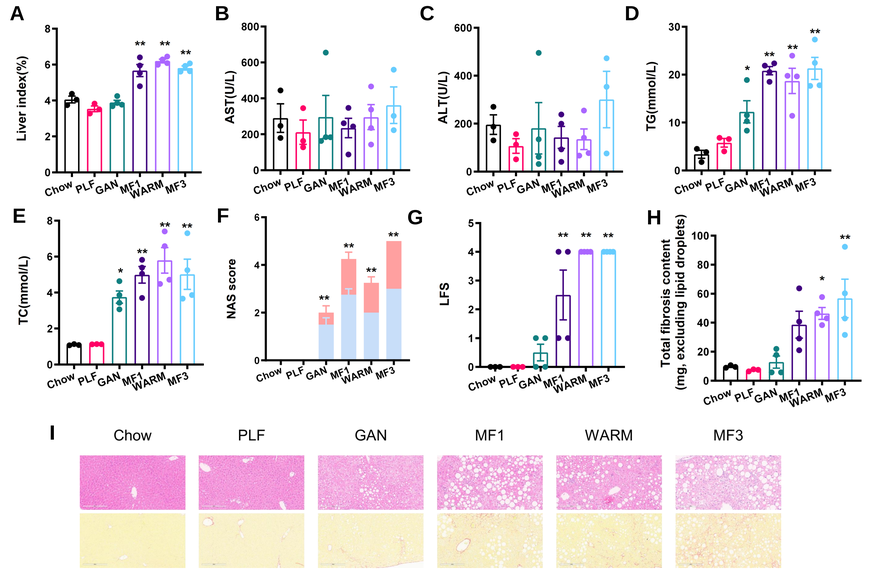

Fig. 2 Optimized formulas (8w) reliably recapitulate MASH in mice. (A) Liver index. (B) Serum AST. (C) Serum ALT. (D) Liver TG. (E) TC. (F) NAS score including steatosis (blue), ballooning (yellow) and inflammation (red). (G) LFS. (H) Quantitative assessment of liver fibrosis based on lipid-free Sirius Red staining. Total fibrosis content was calculated as liver weight x liver fibrosis%. (I) Representative HE and Sirius Red staining results.

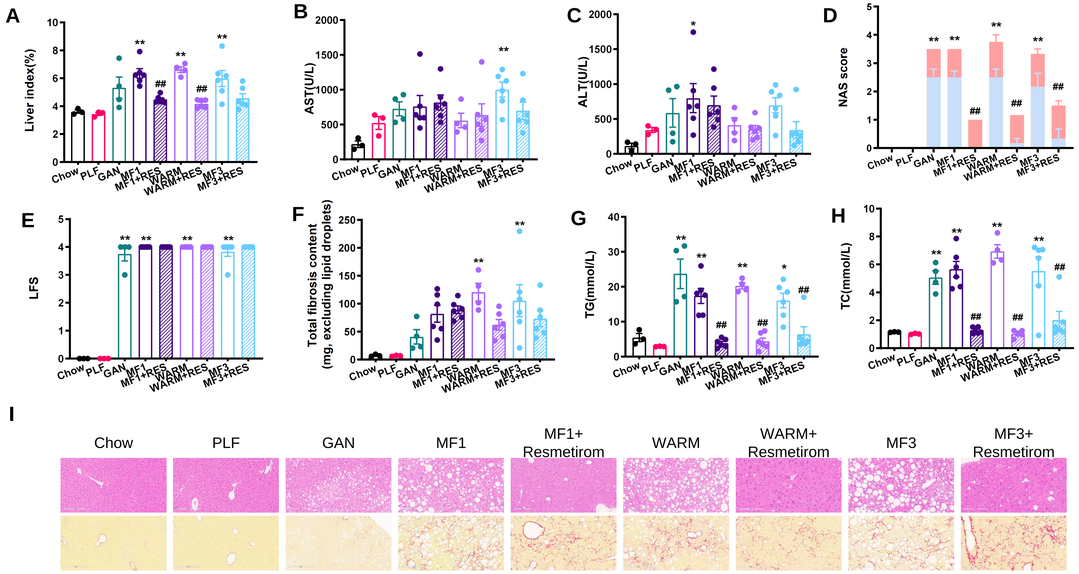

Fig. 3 Resmetirom ameliorates MASH progression in novel diet formula induced MASH mouse model. (A) Liver index. (B) Serum AST. (C) Serum ALT. (D) NAS score including steatosis (blue), ballooning (yellow) and inflammation (red). (E) LFS. (F) Quantitative assessment of liver fibrosis based on lipid-free Sirius Red staining. Total fibrosis content was calculated using liver weight x liver fibrosis%. (G) Liver TG. (H) Liver TC. (I) Representative HE and Sirius Red staining results.

*P < 0.05, **P < 0.01 vs Chow; #P < 0.05, ##P < 0.01 vs. vehicle. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglyceride; LFS, liver fibrosis score. Liver index = liver weight / body weight; Total fibrosis content = SR-positive area × total liver weight

Conclusions

1. Mice fed normal chow or the purified control diet showed no meaningful differences in liver histology or metabolic parameters, although the purified control group had slightly lower serum ALT and AST levels, suggesting that the purified diet matrix itself does not induce hepatic injury.
2. The novel model induced by **WARM diet (D25072905)** reliably induced key features of human MASH, including marked steatohepatitis and accelerated fibrosis, within just 8 weeks—significantly faster than the standard GAN diet induced group. This time-efficient, pathophysiologically relevant platform enhances throughput and translational predictability in preclinical testing.
3. The model demonstrated the robust therapeutic response to Resmetirom, mirroring clinical outcomes, thereby validating its predictive utility for screening anti-MASH and antifibrotic drug candidates.

References

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