Non-alcoholic fatty liver disease (NAFLD) can be effectively treated by weight loss, but identifying the underlying responsible mechanisms has been difficult because of the multifactorial pathophysiology. Quantitative systems pharmacology (QSP) approaches can help overcome this challenge. We developed NAFLDsym, a novel QSP model of NAFLD originally derived from Dilysm, and used it to identify specific mechanisms that may be responsible for reductions in liver triglycerides (TG).

NAFLDsym includes steatosis pathways, lipotoxicity, innate immune responses, hepatocyte turnover, and biomarkers. We created a simulated NAFLD population (SimPops) with inter-individual variability by varying parameters involved in steatosis and lipotoxicity. The SimPops was used to predict reductions in liver TG injury following 6 months of 20% caloric intake restriction. The impact of specific pathways on the predicted reductions in liver TG and lipotoxicity were determined.

Steady (18±14% liver TG) and lipotoxicity (ALT 73±48 U/L) were present in the untreated NAFLD SimPops. Six months of diet treatment resulted in 6.7±1.1 kg reductions in body weight and liver TG absolute reductions of 2.62±0.5%. Plasma ALT was predicted to be normalized in 25% of the NAFLD patients. Decreases in both liver de novo lipogenesis (DNL) and adipose lipolysis were the major contributors to liver TG reductions. VLDL-TG secretion rates also contributed.

NAFLDsym results suggest that dietary intervention is effective in reducing steatosis and lipotoxicity via a combination of effects on hepatic DNL and adipose lipolysis. This analysis may help with interpretation of preclinical and clinical results for NAFLD drugs targeting these pathways when animals or patients are also losing weight.

**RESULTS**

**Overview of Influence of Hypocaloric Diet Effects on Lipids in NAFLDsym**

**Contributions of Plasma FFA and Liver DNL Reductions to Predicted Efficacy in NAFLDsym SimPops**

**Predicted Changes in Liver TG, Plasma ALT, and Body Weight with Diet**

- **Hypocaloric diets (20% reduction over 6 months)** were predicted to reduce body weight by 6.7±1.1 kg and liver TG 2.6±0.5%, the scatter plots show the variability in response across the SimPops.
- **Plasma ALT was also reduced 14±20 U/L.**
- Normalization of plasma ALT (to ≤50 U/L) was achieved in 25% of the SimPops patients, indicating resolution of lipotoxicity.

**Influence of Plasma FFA and Liver DNL Reductions on Predicted Efficacy in NAFLDsym SimPops**

**Effects of weight loss represented in NAFLDsym**

- **Plasma lactate and DNL lipogenesis effects** were validated with data from McMurray 1985 [5].
- **Plasma FFA and adipose FA release effects** were validated with data from Klein 1996 [6].

**Pathophysiologic and Clinical Characteristics of NAFLD SimPops**

**Variables Used to Construct the NAFLD SimPops™**

**REFERENCES**