Using Systems Pharmacology Modeling to Understand the Pathophysiology of NAFLD and Response to Dietary Intervention in a Simulated Population

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ABSTRACT

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 DILIsym, 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 and 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.

Steatosis (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 2.6±2.5%. 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.

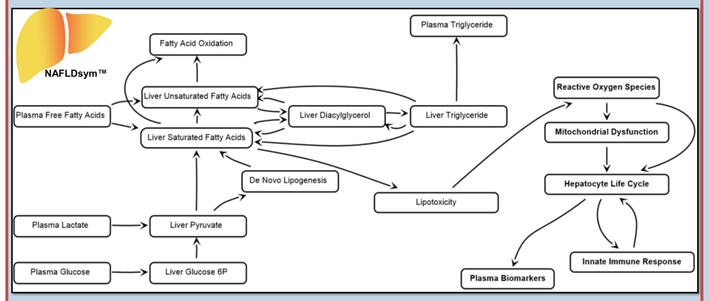
INTRODUCTION

- There is a substantial worldwide incidence of patients with NAFLD, yet there are not effective pharmaceutical treatments currently available for these patients [1]
- NAFLD patients have substantial heterogeneity in pathophysiologic and clinical characteristics
- We have developed NAFLDsym, a QSP model of NAFLD pathophysiology to assist in the development of NAFLD treatments
- Reduced caloric intake has been established to be an effective means of treating NAFLD
- NAFLDsym was used to determine the mechanisms underlying liver triglyceride reductions with hypocaloric diets

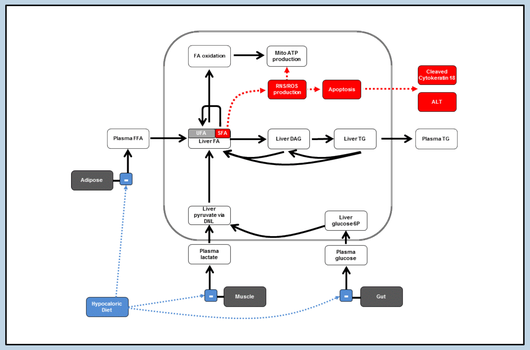
NAFLDsym™

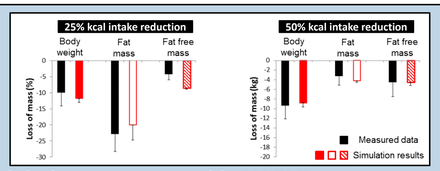
RESULTS

NAFLDsym Overview



Overview of Influence of Hypocaloric Diet Effects on Lipids in NAFLDsym

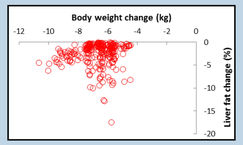


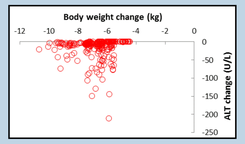


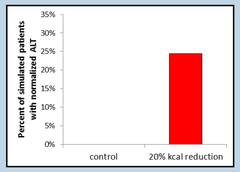
Effects of weight loss represented in NAFLDsym

- Body weight, fat mass, fat free mass effects validated with data from Martin 2011 [2] and Reindardt 2015 [3]; equations from Hall 2009 [4]
- Plasma lactate and DNL lipogenesis effects optimized with data from McMurray 1985 [5]
- Plasma FFA and adipose FA release effects optimized with data from Klein 1996 [6]

Predicted Efficacy in NAFLDsym SimPops



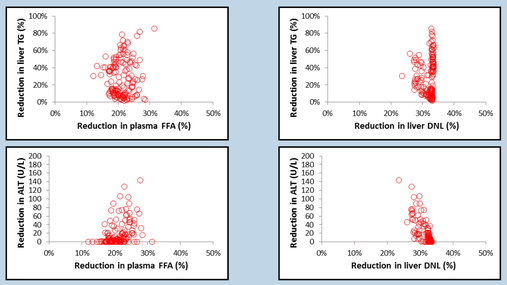




Predicted changes in liver TG, plasma ALT, and body weight with diet

- Hypocaloric diets (20% reduction over 6 months) were predicted to reduce body weight 6.7±1.1 kg and liver TG 2.6±2.5%; the scatter plots show the variability in response across the SimPops.
- Plasma ALT was also reduced 14±26 U/L.
- Normalization of plasma ALT (to ≤40 U/L) was achieved in 25% of the SimPops patients, indicating resolution of lipotoxicity.

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



Influence of plasma FFA and liver DNL reductions on predicted liver TG and plasma ALT responses to diet

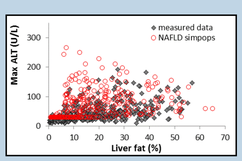
- Reductions in both plasma FFA and liver DNL are required to provide maximal efficacious benefit from diet treatment for NAFLD patients.
- The substantial underlying inter-patient variability in DNL contributes to heterogeneity in predicted efficacy

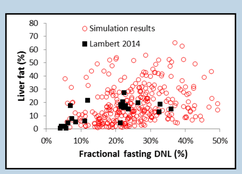
Pathophysiologic and Clinical Characteristics of NAFLD SimPops

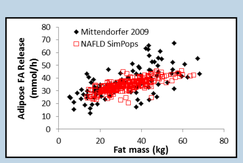
Construction and validation of NAFLD SimPops

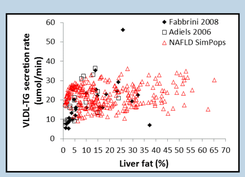
- Simulated NAFLD patients (n=304) include combinations of parameter ranges based on reported responses from literature [7,8,9,10,11,12].
- Simulated patients within SimPops have pathophysiologic and clinical characteristics consistent with the literature, including liver TG, plasma ALT, VLDL-TG secretion rates, adipose FA release, liver DAG, liver oxidative stress, distribution of BMI amongst simulated patients, and fraction of simulated patients with type 2 diabetes [7,8,9,10,11,12].
- Simulated patients have appropriate responses to meals, as evidenced by predicted plasma glucose, FFA, and TG levels over 24 hours.

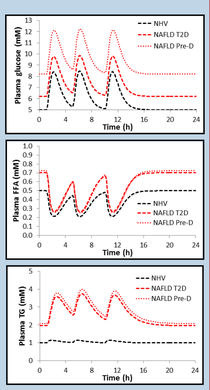
Variables Used to Construct the NAFLD SimPops™
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration











METHODS

Overview NAFLDsym was utilized for all simulations. NAFLDsym includes a representation of the primary pathways controlling liver fatty acid and triglyceride fluxes in addition to the effects of lipotoxicity on hepatocellular health. ALT and cK18, biomarkers of hepatocellular loss, are also represented. Simulated levels of liver and plasma TG are also outputs of NAFLDsym.

Simulated Patients A simulated population of patients with the pathophysiological aspects of NAFLD are included in NAFLDsym. This SimPops (n=304) includes a number of characteristics that are consistent with the observed heterogeneity of pathophysiologic and clinical features of NAFLD.

Simulated Effects of Hypocaloric Diets Reduced caloric intake has been shown to lead to concomitant reductions in body weight [4]. This has been modeled previously by Hall et al. [4], and these published equations were utilized to predict body weight and adipose mass changes in NAFLDsym. Mechanistically, reduced caloric intake could influence hepatic steatosis by reducing the amount of substrate available for de novo lipogenesis [5] in addition to reducing adipose mass [2,3]; reduced adipose mass has been shown to further reduce adipose lipolysis and the release of fatty acids to the circulation [6].

Simulated Protocols Hypocaloric diets (20% caloric reduction) were simulated in the SimPops for 6 months. Predicted changes in de novo lipogenesis, adipose fatty acid release, liver TG, plasma ALT, and body weight were the primary simulation results used for these analyses.

CONCLUSION

- Hypocaloric diets are effective at reducing liver triglycerides due to their effects to reduce liver DNL and adipose lipolysis
- These mechanisms should be taken into consideration when interpreting clinical data where there is weight loss in addition to drug effects

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