



SimulationsPlus

MIDD+22

Model Informed Drug Development

Yo-Yo Dieting Predicted to Contribute to Fibrosis Score Reductions in Untreated (Placebo) Cohorts




Lisl KM Shoda



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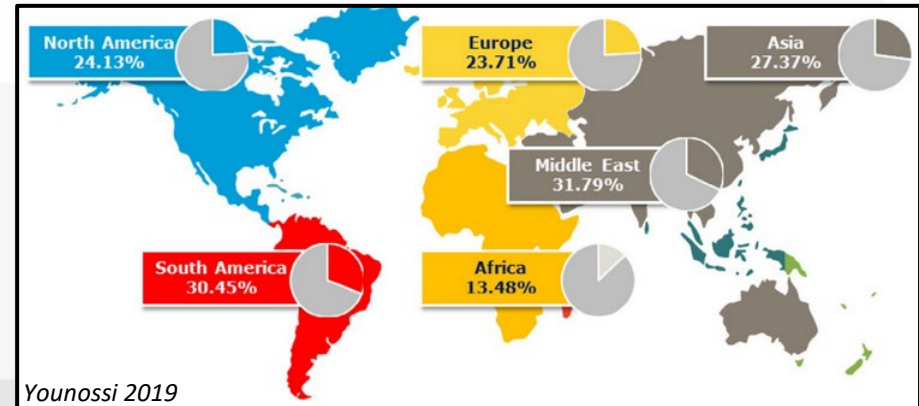
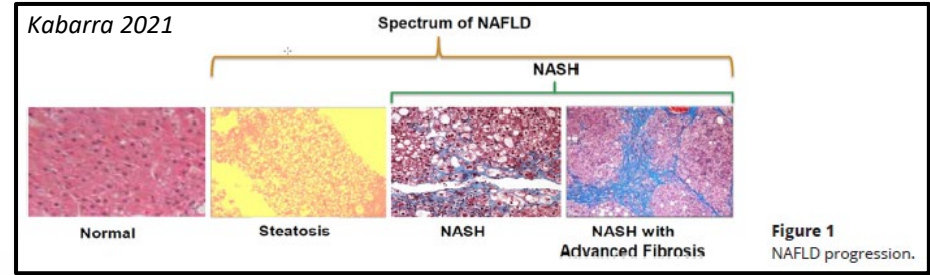


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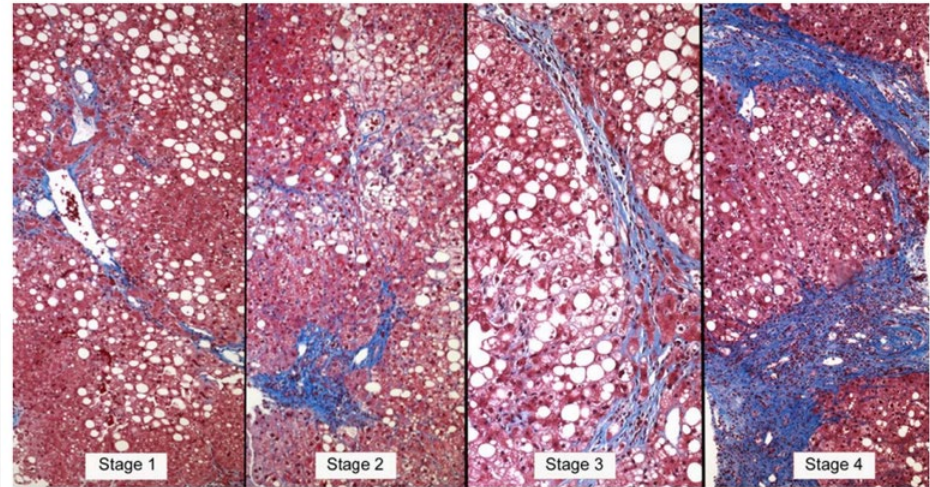
Non-alcoholic Fatty Liver Disease (NAFLD) / Non-alcoholic Steatohepatitis (NASH)

- NAFLD/NASH represents a spectrum of chronic liver disease
- Global prevalence is estimated at ~25% in the adult population with no approved drug treatment
 - Substantial opportunity to improve health for many patients by developing treatments



Histopathological Endpoints in NAFLD/NASH

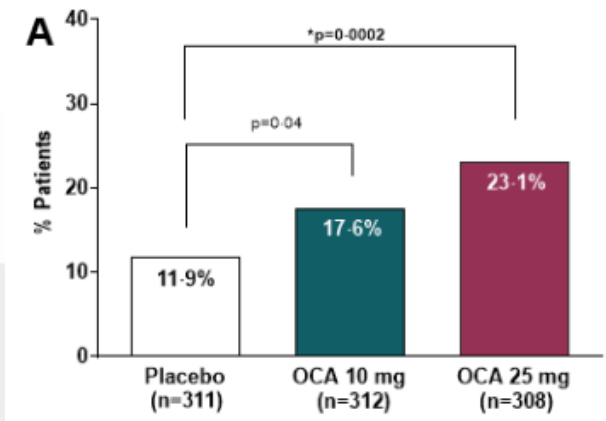
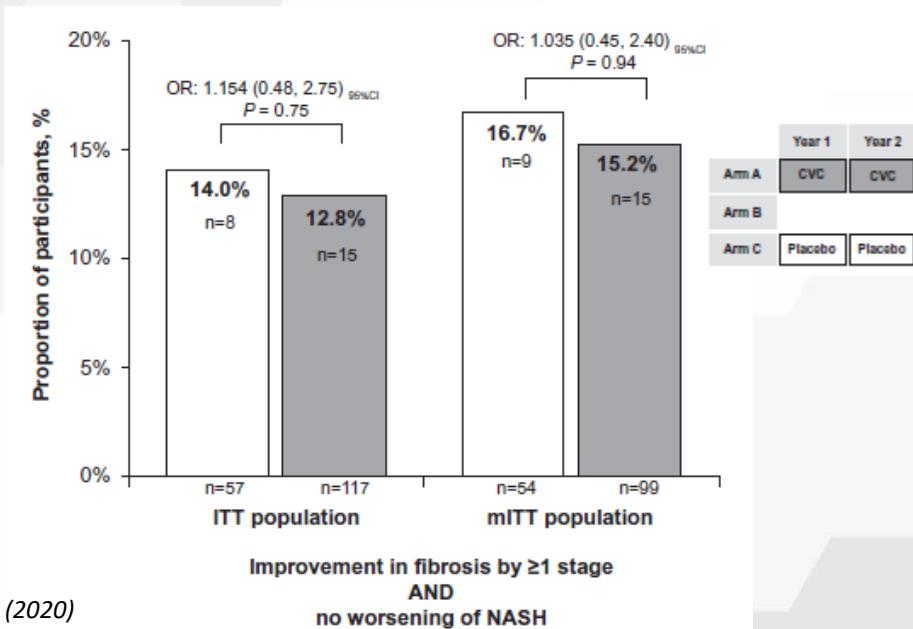
- Liver biopsy is the definitive technique for diagnosis and classification of NAFLD
- NAFLD Activity Score (NAS), a summary score ranging from 0-8, developed to grade key features of steatosis, hepatocellular ballooning, and lobular inflammation
- Fibrosis, representing disease stage, scored separately



Younossi 2018

In Clinical Trials, 10-20% of Placebo-Treated Patients Demonstrate Fibrosis Improvement

- Randomized, placebo-controlled clinical trials with biopsy proven NASH/NAFLD, in which biopsies were collected to evaluate clinical endpoints



Proportion of patients w/improvement ≥ 1 stage
AND
no worsening of NASH in the ITT population

Ratziu (2020)

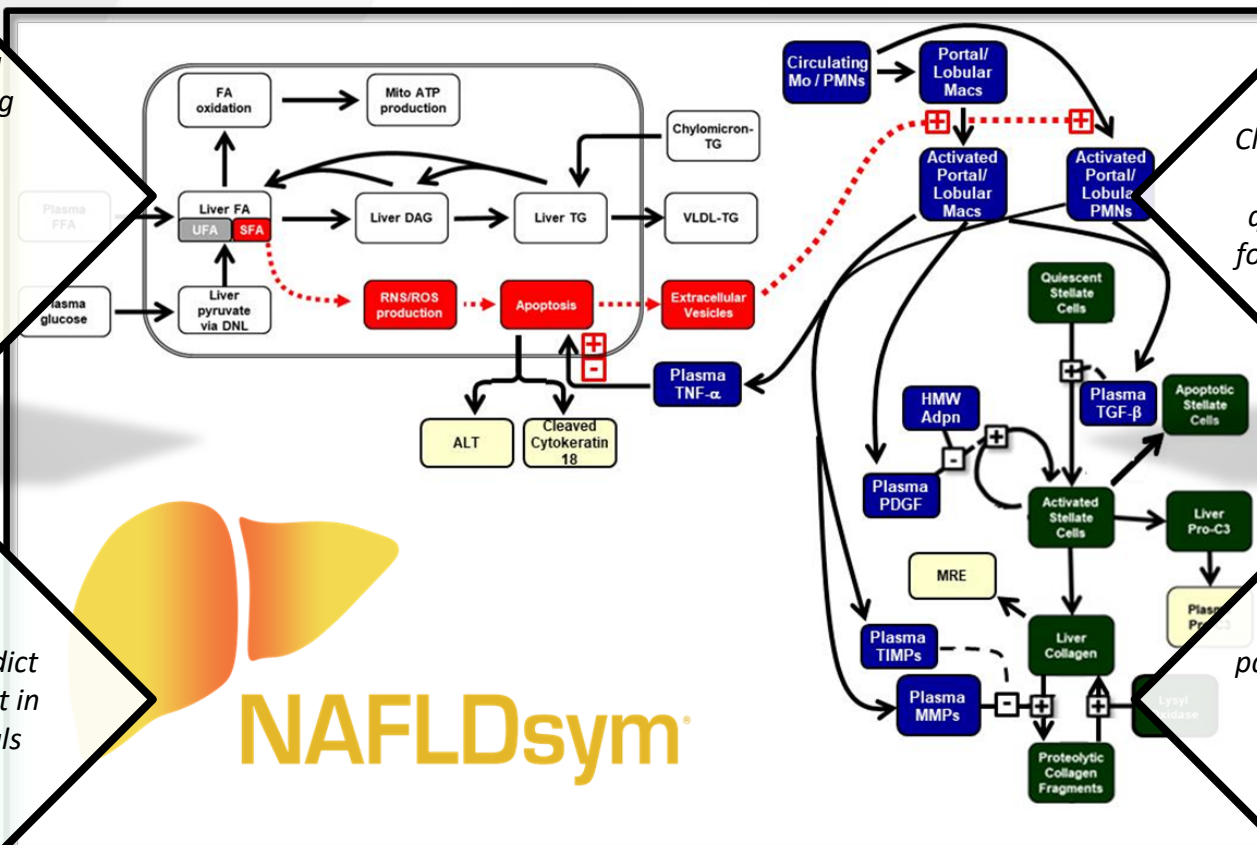
Younossi (2019)

***What might account for fibrosis improvement
in the placebo-treated groups?***

NAFLDsym, a QSP Model of NAFLD, is Uniquely Positioned to Address this Question

Multiple interacting sub-models, including

- Steatosis
- Lipotoxicity
- Inflammation
- Fibrosis
- Biomarkers
- Weight gain/loss



Clinical data from literature used to establish quantitative relationships for underlying biochemistry



NAFLDsym

Provides ability to predict responses to treatment in simulated clinical trials

Numerous simulated patients (SimPops) included to account for pathophysiologic and clinical heterogeneity

NAFLDsym Previously Applied to Explore Disease Progression and Weight Loss

Virtual Patient Generation Strategies for Non-Alcoholic Fatty Liver Disease

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RESULTS

Simulations of Disease Progression within NAFLDsym

- 2% increase in caloric intake over 20 years resulted in ~20-30% body weight gain by design¹⁷.
- Liver fat levels of some patients have increased fast and reached a steady state, while some showed a slow and steady increase.
- Varying the aforementioned parameters allowed simulation of inter-patient variability in progression of NAS score and Fibrosis stage.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are of growing concern across developed countries, with recent estimates suggesting up to 30% of the US population may be affected. NAFLDsym v2a is a QSP model of NAFLD and NASH that represents the primary pathophysiological components of the disease, including steatosis, lipotoxic inflammation, oxidative stress, hepatocyte apoptosis, hepatocellular carcinoma, and fibrosis. The model consists of a system of ordinary differential equations (ODEs) and stochastic processes that describe the underlying biology of these processes. The model is used to generate virtual patients, each with its own disease progression, which can be used to explore the impact of various interventions on disease progression.

Simulations of Disease Progression within NAFLDsym

- 2% increase in caloric intake over 20 years resulted in ~20-30% body weight gain by design¹⁷.
- Liver fat levels of some patients have increased fast and reached a steady state, while some showed a slow and steady increase.
- Varying the aforementioned parameters allowed simulation of inter-patient variability in progression of NAS score and Fibrosis stage.

ACOP10 (2019)

DLISym Services
 SIMULATED PATIENTS

Bristol-Myers Squibb

Identification of NASH patient characteristics associated with fibrosis response to weight loss using a QSP approach

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 QSP and PBPK, Clinical Pharmacology and Pharmacometrics, Bristol-Myers Squibb
 Current affiliation: Bristol Myers Squibb

PIIA-028
 Bristol Myers Squibb

Abstract

Objectives: Understanding the impact of the pathophysiological mechanisms on the inter-patient variability in disease progression and in the response to therapeutic or lifestyle interventions. The goal of this study was to design new therapies and identifying the patient population that can benefit from a therapy. In this study, we employed a quantitative systems pharmacology (QSP) approach to build such understanding for NAFLD and NASH.

Methods: The virtual population for NASH was developed using deterministic disease progression simulations with NAFLDsym v2a, a QSP model for NAFLD and NASH [1], and was validated with the clinical data from dietary intervention studies (ACOP12, QSP72). We explored the relationship between fibrosis response to weight loss and the virtual patient characteristics and disease history using the developed virtual population.

Results: The dietary intervention simulations with the calibrated virtual NASH cohort (P1-P4) predicted significant inter-patient variability in changes of clinical biomarkers and histology endpoints (Figure 2). Some virtual patients showed rapid fibrosis stage reduction, while fibrosis remained stable or worsened for other virtual patients despite substantial weight loss. We found that fibrosis response rate due to weight loss correlated with virtual patient parameters related to the sensitivity of inflammatory and fibrosis processes to perturbation in lipid metabolism (Figure 3). We also explored links between the fibrosis response rate and features of patient disease history. The prediction suggested that the longer time a patient spent in the baseline fibrosis stage before the treatment, the less likely the patient response to dietary intervention (Figure 4) however, disease progression rate at a virtual start at the start of treatment showed some correlation with fibrosis response, but the correlation was not statistically significant (Figure 4).

Conclusions: QSP approach presented here provides interesting insights on the patient characteristics. Features of patient history, such as the time spent in baseline fibrosis stage, are important for fibrosis response to weight loss. NAFLDsym and the predicted changes in biomarkers can be used for identification of patient population for clinical trials.

NAFLDsym QSP model

Interpatient Variability in Response to Weight Loss

Figure 2. Predicted interpatient variability in responses to weight loss

Virtual Patient Characteristics Associated with Fibrosis Response to Weight Loss

Figure 3. VP characteristics that are associated with fibrosis response to weight loss

Features of Virtual Patient History Associated with Fibrosis Response to Weight Loss

Figure 4. VP history affects the fibrosis response to weight loss

ACOP12 (2021)

Interpatient Variability in Response to Weight Loss

Figure 2. Predicted interpatient variability in responses to weight loss

The central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the '+' symbol

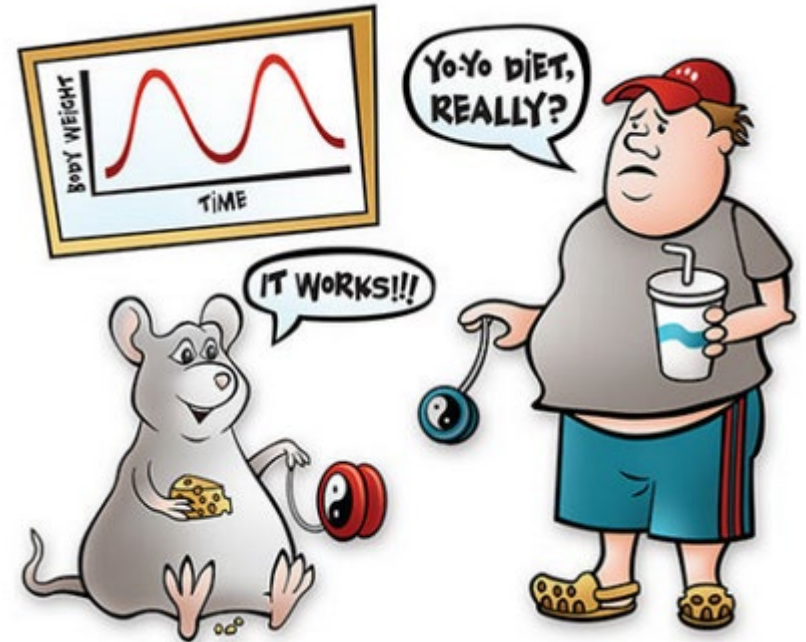
52 weeks of dietary intervention simulations targeting 5-10% weight loss in NASH Vpop (n=825) and resulted in varying degree of changes in key biomarkers such as liver fat content, plasma ALT, liver collagen and serum ProC3. The predicted changes in histology endpoints such as NASH and fibrosis stage also varied from VP to VP. Please note that liver fat reduction, plasma ALT and NASH was used in calibration (ACOP12 QSP72).

ACOP12 (2021)

What if patient behavior (particularly diet) in the placebo group is influenced by being in the clinical trial?

Periodic Weight Cycling in Response to Changing Diet/Activity is Known as Yo-Yo Dieting

- Intentional weight loss followed by unintentional weight regain is a relatively common occurrence
- Although this weight cycling has been associated with morbid health conditions and increasing mortality, recent analyses and data argue against purely adverse effects (Smith 2018, Mehta 2014)
- **Hypothesis:** In a clinical trial, unintentional weight loss may occur in anticipation of upcoming regular clinic visits, followed by unintentional weight gain after the visit



Di Garmanio (2018)

Simulated Yo-Yo Dieting in Otherwise Untreated SimCohorts

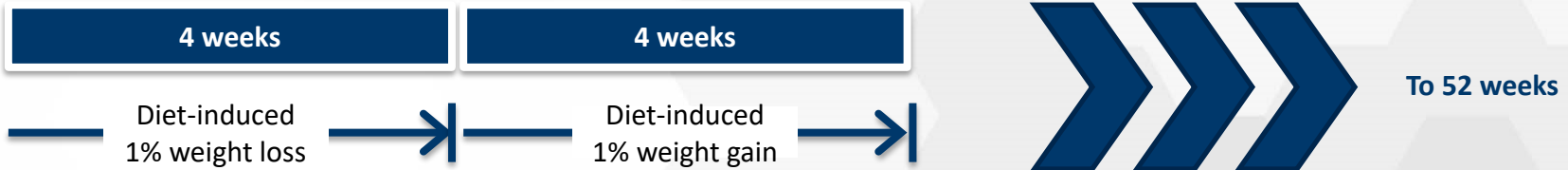
SimCohorts represent inter-patient variability



Baseline characteristics of N=90 SimCohorts

Body weight (kg)	Liver fat (%)	Plasma ALT (U/L)	NAS (score)	F2 Fibrosis (%)	F3 Fibrosis (%)
89.1 ± 19.4	17 ± 5	50 ± 12	5.6 ± 3.2	35/90 (39)	55/90 (61)

Simulation plan:



Simulations Predict Yo-Yo Dieting Can Reduce Fibrosis Scores Similar to Clinical Reports

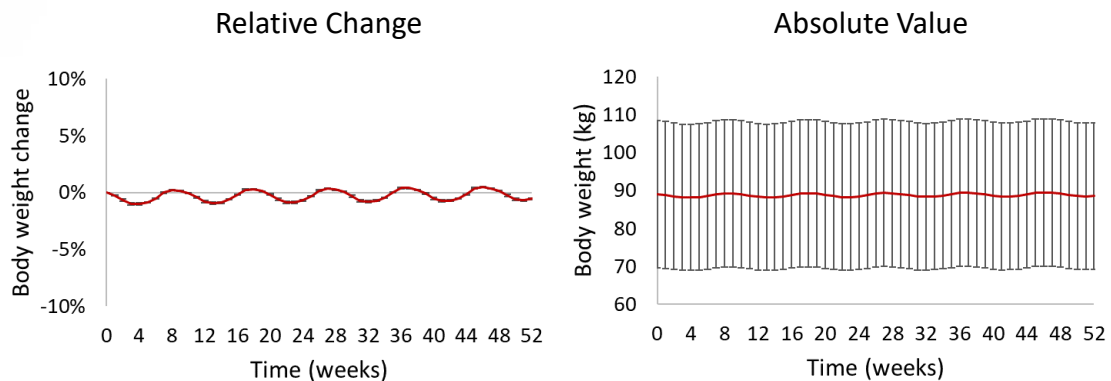
- Successive cycles of mild (1%) weight loss and weight gain are predicted to persistently reduce fibrosis scores in ~10% of subjects
- By contrast, the NAFLD activity score (NAS) reflecting histologic measures of steatosis, lobular inflammation, and ballooning, is predicted to be largely unchanged

Predicted Histologic Reductions

Time (weeks)	Fibrosis reduction ≥ 1 stage (%)	NAS reduction ≥ 2 points (%)
13	6	4
26	10	0
39	12	0
52	10	0

Predicted Dynamic Changes in Body Weight Confirm Yo-Yo Dieting in SimCohorts

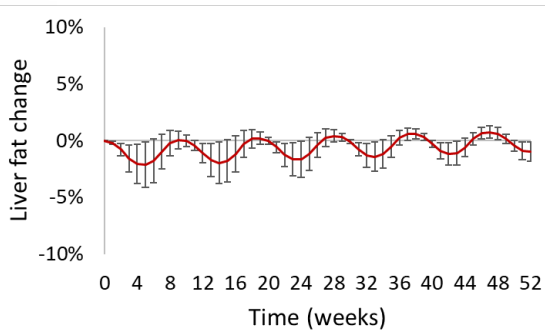
- Mean body weight oscillates by ~1% every 4 weeks by design
- Absolute body weight measurements demonstrate mild oscillations that would likely be clinically undetectable



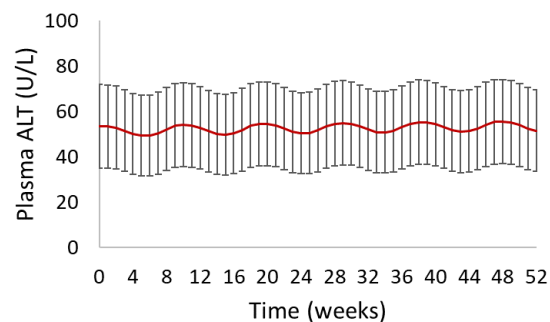
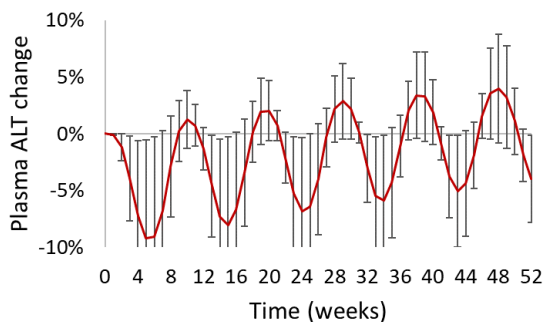
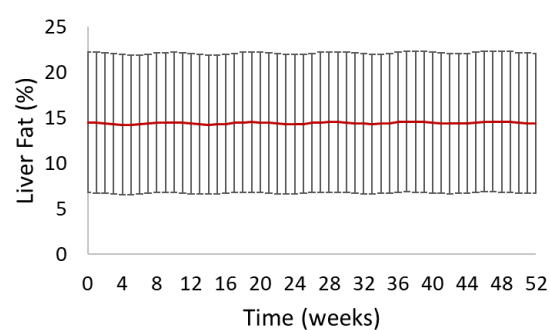
Predicted Changes in Liver Fat and ALT Illustrate Dynamic Changes That Mirror Weight Change

- Liver fat and ALT oscillate on similar time scales as diet
- Absolute changes are relatively minor but might be detected depending on timing of measurement

Relative Change

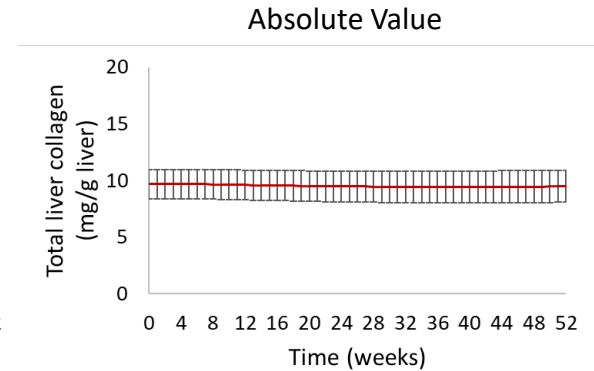
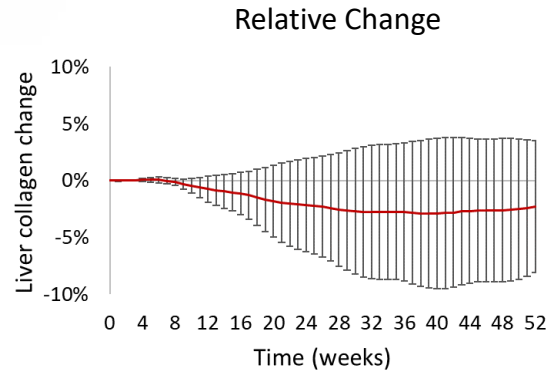


Absolute Value



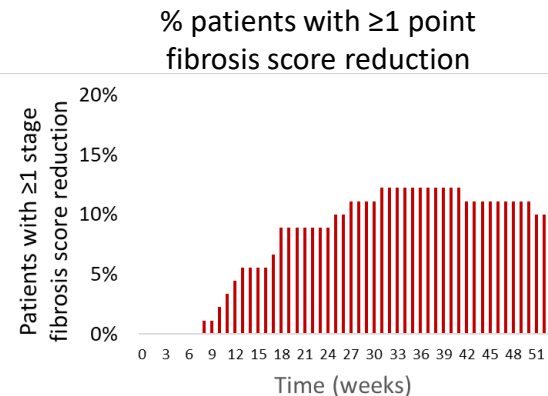
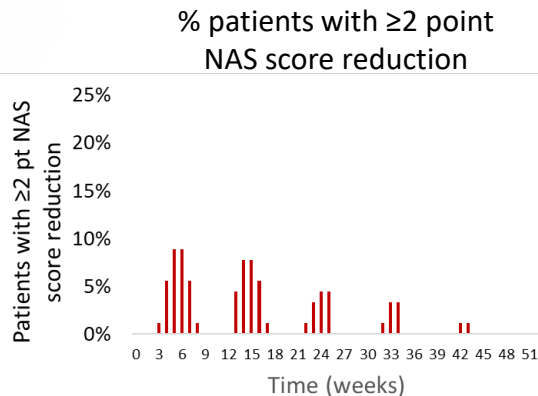
Predicted Changes in Liver Collagen Illustrate Different Dynamics for Fibrotic Response

- Changes in fibrosis reflect slower dynamics than those related to steatosis or lipotoxicity
- Absolute changes are modest
- Fibrosis scores reflect amount and location of collagen in the hepatic acinus



Clinical Endpoints are Differentially Affected by Fast vs. Slow Dynamics

- Measurement timing more likely affects endpoints governed by fast dynamics



Conclusions

- Yo-yo dieting could contribute to relatively high placebo cohort fibrosis response rates in NASH clinical trials
- Reductions in fibrosis score are due to the slow rate of change of collagen relative to steatosis and lipotoxicity
- Change in fibrosis manifests over time with continued yo-yo dieting
- Depending on timing of measurement, changes in liver fat and plasma ALT may be detectable in patients undergoing yo-yo dieting

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Yo-Yo Dieting Predicted to Contribute to Fibrosis Score Reductions in Untreated (Placebo) Cohorts

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AASLD Nov 12-15, 2021
The Liver Meeting
DIGITAL EXPERIENCE

INTRODUCTION

10-25% of the patients in placebo cohorts in NAFLD clinical trials (3-5.2 years) have fibrosis score reductions. What could be mechanistically responsible for improvements in fibrosis scores in such high proportions of untreated patients? Reduced caloric intake can minimize hepatic lipid burden, yet weight loss was not reported at the end of these studies. Cyclic alterations in caloric intake or yo-yo dieting may be able to explain the clinical observations.

AIM

Use mathematical modeling to evaluate the merits of the hypothesis that yo-yo dieting may exist changes in histologic endpoints in placebo cohorts of clinical NAFLD studies.

MATERIAL & METHODS

Mathematical modeling with a quantitative systems pharmacology model, NAFLDsymTM, was used. Simulations were performed in NAFLDsym Cohorts (N=60, Table 1). The SimCohorts were subjected to alterations in food intake first led to the loss of body weight over 4 weeks followed by a return to baseline body weight over the following 4 weeks. This yo-yo pattern of weight loss and gain was repeated over one year in the otherwise untreated simulated patients.

RESULTS

Predicted Histologic Reductions

	13 weeks	26 weeks	39 weeks	52 weeks
NAFL	6%	16%	12%	16%
NAFL2	4%	6%	6%	6%

Table 2: Treatment of macrophage with pravastatin fibrosis score (p) and total cholesterol (p) at the respective time points due to yo-yo dieting.

NAFLDsym Overview

Figure 1: Overview of NAFLD mechanisms modeled in DILIsym, NAFLDsym.

SimCohorts Baseline Characteristics

Characteristic	Value
Age (years)	50.0
Weight (kg)	85.0
Height (cm)	175.0
BMI (kg/m ²)	27.5
ALT (U/L)	45.0
AST (U/L)	35.0
ALP (U/L)	120.0
Gamma-GT (U/L)	60.0
Cholesterol (mg/dL)	200.0
Triglycerides (mg/dL)	150.0
Fasting Glucose (mg/dL)	100.0
Hemoglobin A1c (%)	5.7

Table 1: Characteristics of NAFLD SimCohorts (N=60) used in NAFLDsym simulations.

Figure 2: Predicted relative changes (left) and absolute losses (right) of body weight over the placebo 52-week time course with yo-yo dieting. Note the effectiveness in timing of each output in response to fluctuating (yo-yo) caloric intake.

CONCLUSIONS

- Yo-yo dieting could contribute to high placebo cohort response rates in NAFLD clinical trials.
- Small, cyclic changes in caloric intake (yo-yo dieting) can elicit fibrosis score reductions in NAFLD patients.
- Reductions in fibrosis score are due to the slow rate of change of collagen relative to steatosis and lipofuscin.
- Changes in fibrosis manifests over time with continued yo-yo dieting.
- Depending on timing of measurement, changes in liver fat and plasma ALT may be detectable in patients undergoing yo-yo dieting.

REFERENCES

1. Rubin V, Heneghan MF. *N Engl J Med*. 2019; 381(25):2468-2477.
2. S. Q. Siler et al. *Hepatology*. 2019; 69(5):1813-1824.
3. Apolunig V, et al. *ASAP* 2019.

DISCLOSURES

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CONTACT INFORMATION

For further information or questions, please contact Lisi Shoda at lisishoda@simulationsplus.com.

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Q&A

Questions & Answers

