

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

Lisl KM Shoda, Christina Battista, Grant T Generaux, Scott Q Siler

DILsym Services Division, Simulations Plus Inc., Research Triangle Park, NC

**DIGITAL EXPERIENCE**

## INTRODUCTION

10-25% of the patients in placebo cohorts in NASH clinical trials (0.5-2 years) have fibrosis score reductions<sup>1</sup>. 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. Cyclical 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 elicit changes to histologic endpoints in placebo cohorts of clinical NASH studies

## MATERIAL & METHODS

Mathematical modeling with a quantitative systems pharmacology model, NAFLDsym<sup>2-3</sup>, was used. Simulations were performed in NASH SimCohorts (n=90, Table 1). The SimCohorts were subjected to alterations in food intake that led to 1% 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 applied over one year in the otherwise untreated simulated patients.

## RESULTS

Predicted Clinical Changes with Yo-yo Dieting

Predicted Histologic Reductions				
	13 weeks	26 weeks	39 weeks	52 weeks
<b>Fibrosis</b>	6%	10%	12%	10%
<b>NAS</b>	4%	0%	0%	0%

Table 2. Fractions of SimCohorts with predicted fibrosis score (≥1 pt) and NAS reductions (≥2 pts) at the respective time points due to yo-yo dieting

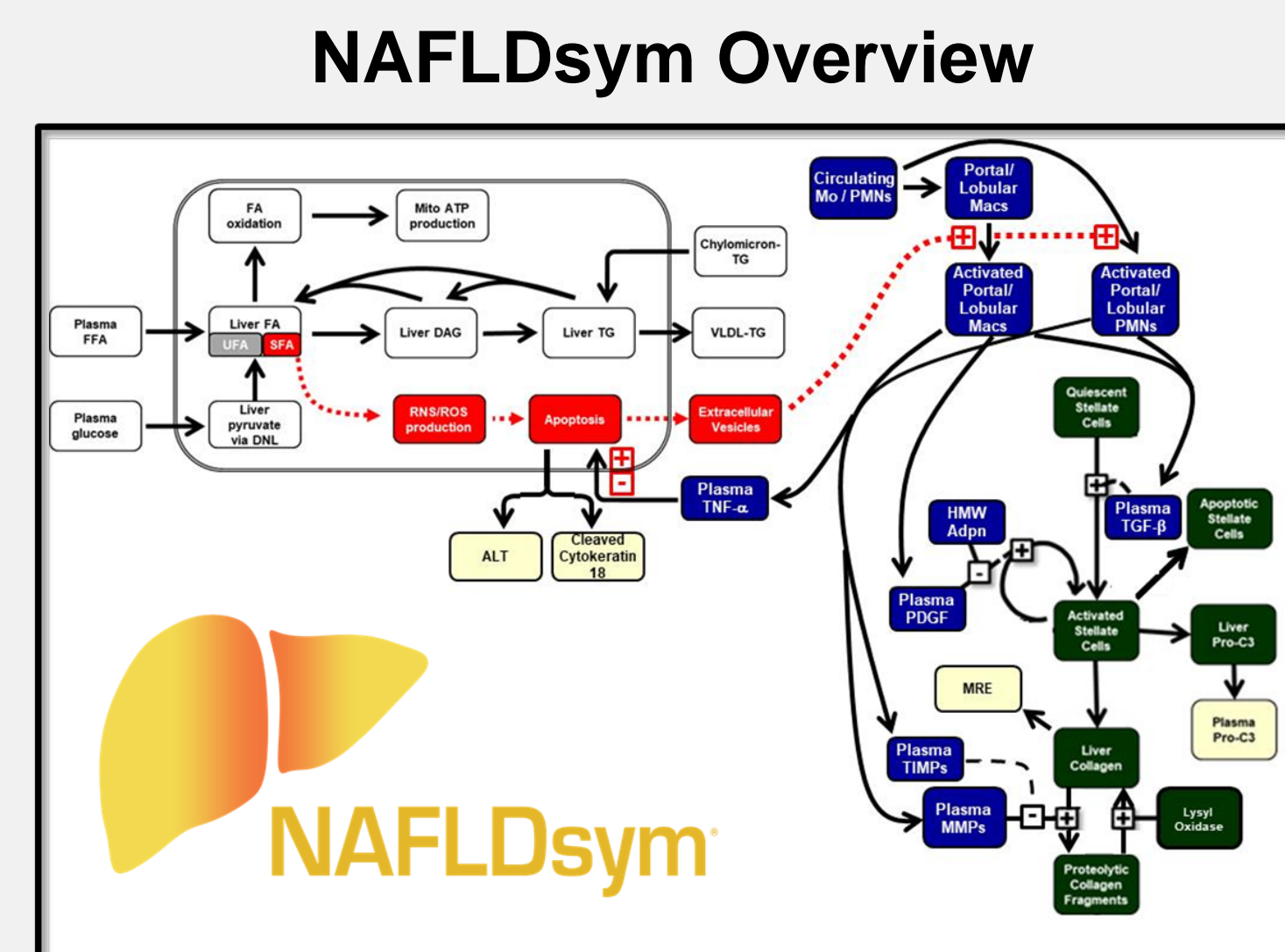


Figure 1. Overview of NASH mechanisms included in QSP model, NAFLDsym.

SimCohorts Baseline Characteristics

Baseline SimCohorts Characteristics					
Body weight (kg)	Liver fat (%)	Plasma ALT (U/L)	NAS (score)	Fibrosis score = 2	Fibrosis score = 3
89.1±19.4	17±5	50±12	5.6±3.2	39%	61%

Table 1. Characteristics of NASH SimCohorts (n=90) used in NAFLDsym simulations

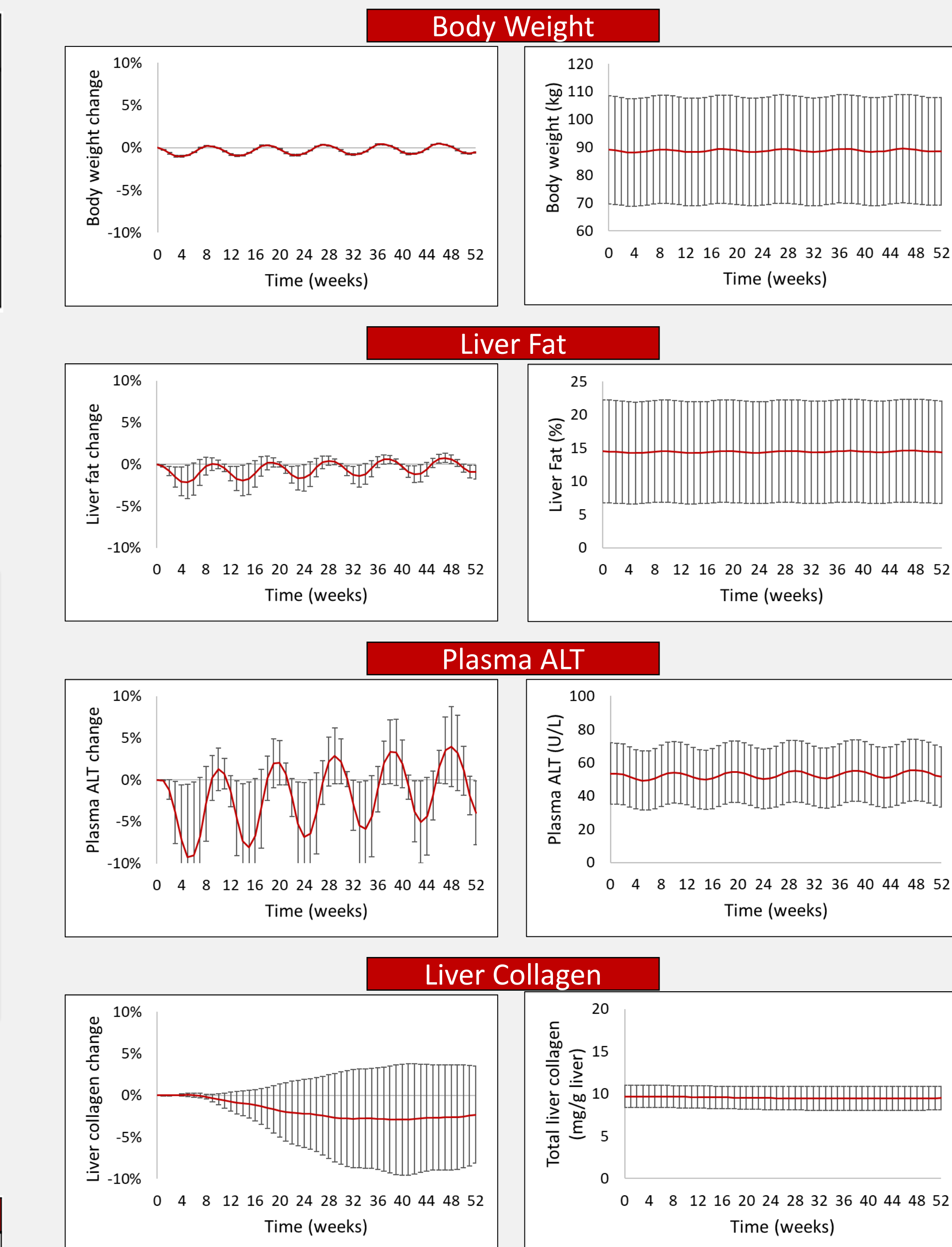


Figure 2. Predicted relative changes (left) and absolute levels (right) of body weight, liver fat, plasma ALT, and liver collagen over time due to yo-yo dieting. Note the differences in timing of each output in response to fluctuating (yo-yo) caloric intake.

## CONCLUSIONS

- Yo-yo dieting could contribute to high placebo cohort response rates in NASH clinical trials
- Small, cyclical changes in caloric intake (yo-yo dieting) can elicit fibrosis score reductions in NASH patients
- 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

## REFERENCES

- Ratzliff V, Hepatology, vol. 72, no. 3, p. 892, (2020)
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- Akpınar Singh, FA, et al., ACoP 2019

## DISCLOSURES

LKMS, CB, GTG, SQS are employees of Simulations Plus

## CONTACT INFORMATION

For further information or questions, please contact Lisl Shoda at [lisl.shoda@simulations-plus.com](mailto:lisl.shoda@simulations-plus.com)

