Implementation of a Physiologically Based Pharmacokinetic Modeling Approach to Predict Disease-Related Changes in Drug Pharmacokinetics in Patients with Nonalcoholic Fatty Liver Disease

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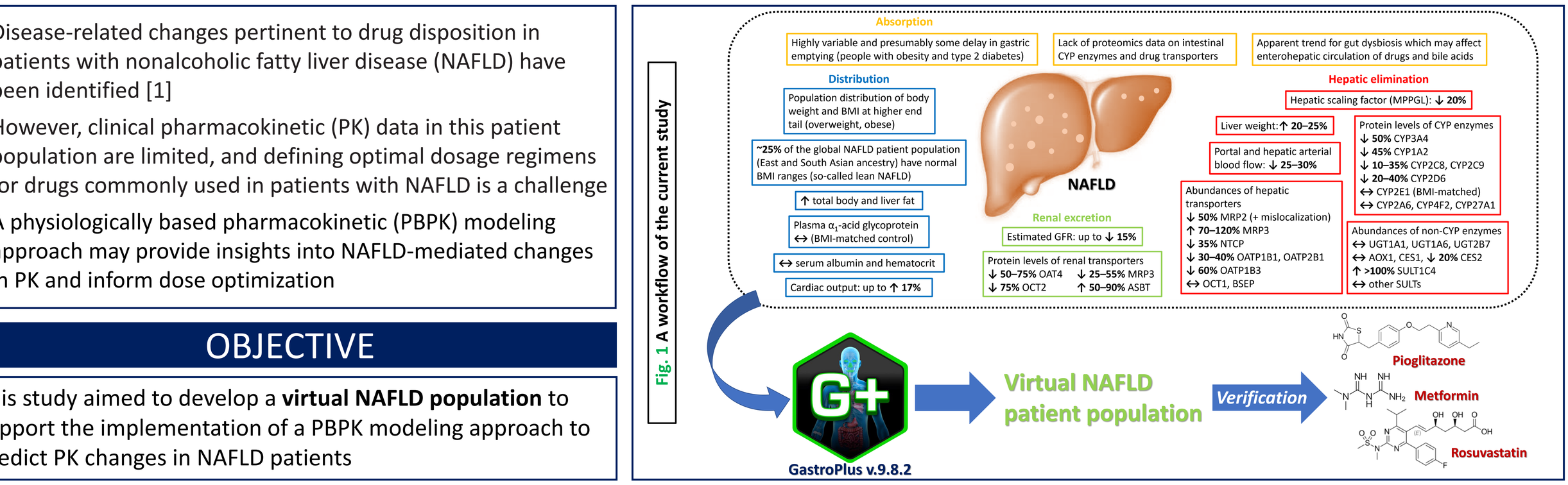
INTRODUCTION

- Disease-related changes pertinent to drug disposition in patients with nonalcoholic fatty liver disease (NAFLD) have been identified [1]
- However, clinical pharmacokinetic (PK) data in this patient population are limited, and defining optimal dosage regimens for drugs commonly used in patients with NAFLD is a challenge
- A physiologically based pharmacokinetic (PBPK) modeling approach may provide insights into NAFLD-mediated changes in PK and inform dose optimization

OBJECTIVE

This study aimed to develop a **virtual NAFLD population** to support the implementation of a PBPK modeling approach to predict PK changes in NAFLD patients

METHODOLOGY



OBJECTIVE

This study aimed to develop a **virtual NAFLD population** to support the implementation of a PBPK modeling approach to predict PK changes in NAFLD patients

RESULTS

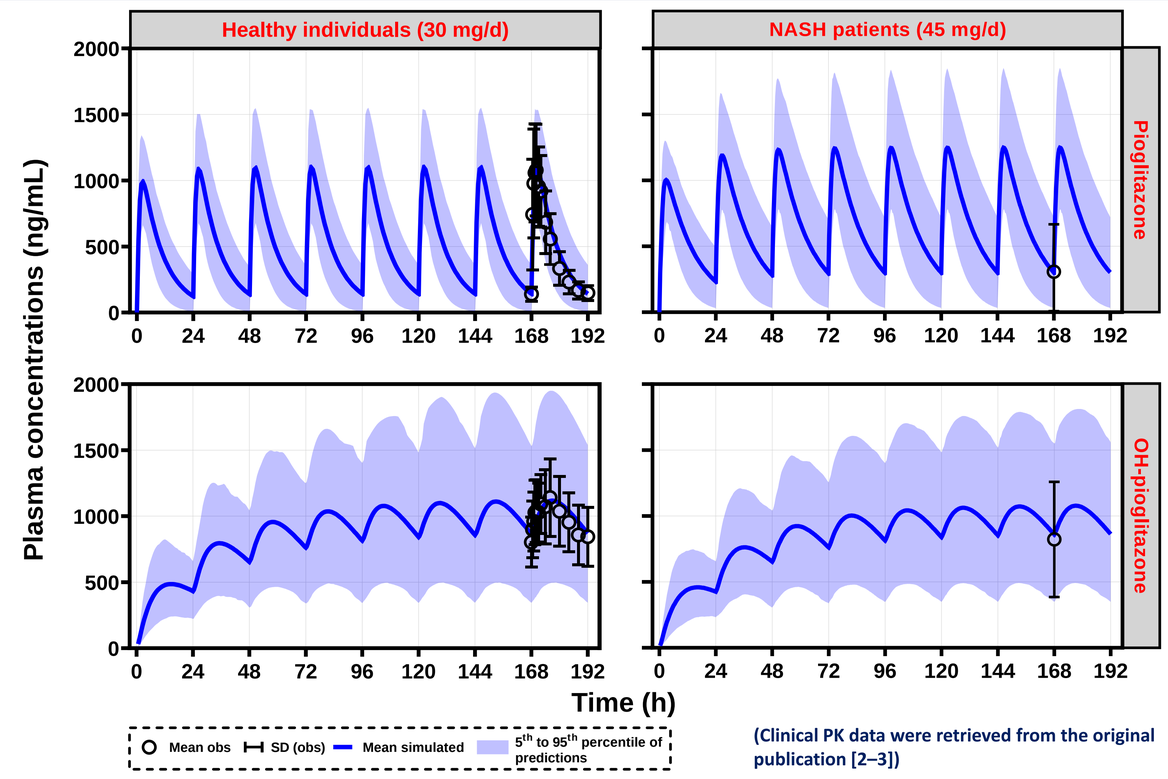


Fig. 2 Comparison of PBPK model predictions and clinically-observed concentrations of pioglitazone and the active metabolite, hydroxy-pioglitazone in healthy people and patients with NASH

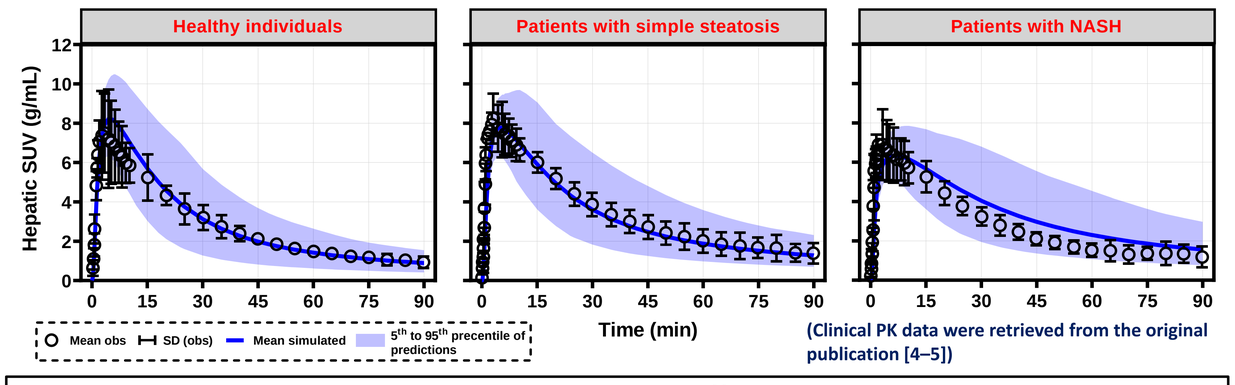


Fig. 3 Verifications of the virtual NAFLD population using ^{11}C-metformin as an exemplar compound

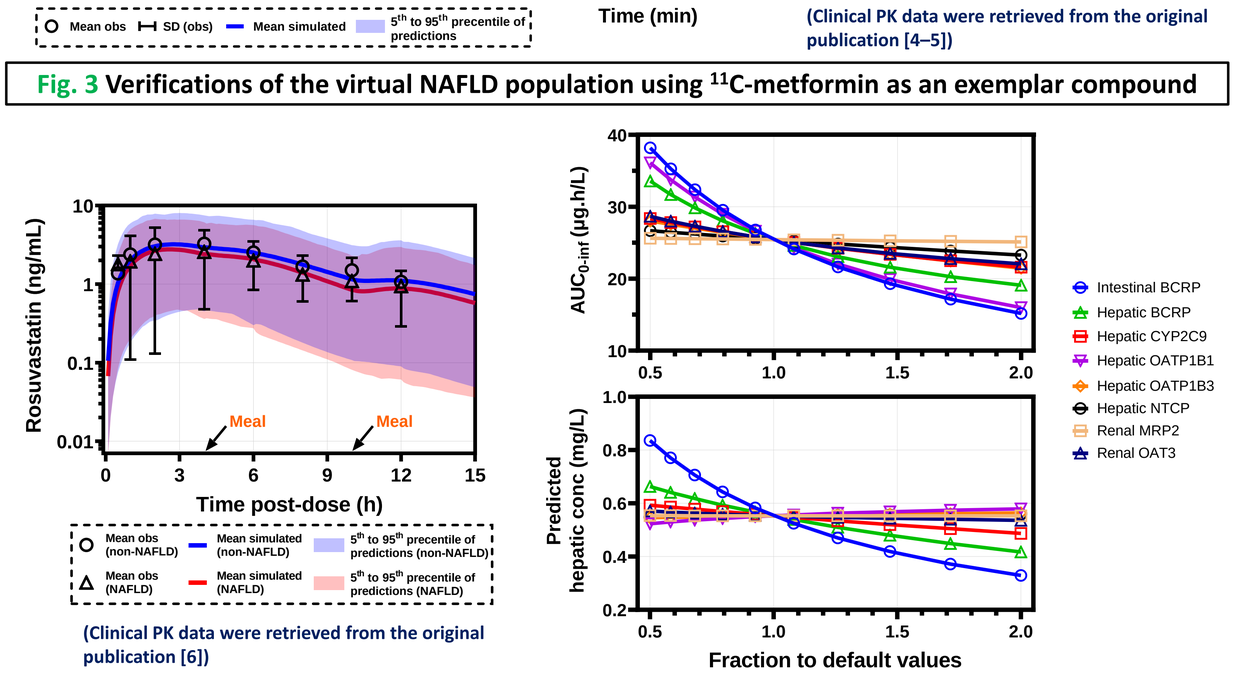


Fig. 4 Verifications of the virtual NAFLD population using rosuvastatin (5 mg) as an exemplar compound, and sensitivity analyses (variation of drug transporter abundance) in healthy individuals

Table 1 Simulated and clinically-reported values [2–6] for pharmacokinetic parameters of the selected compounds used to verify the virtual NAFLD population

Compound	Parameter	Ratio (diseased population divided by healthy control)		Prediction-fold difference
		Model prediction	Clinically-reported value	
Pioglitazone	Dose-normalized trough concentration ($C_{ss,min}$)	1.42	1.46	0.97
OH-pioglitazone		0.66	0.68	0.97
^{11}C-metformin	Peak hepatic SUV (simple steatosis)	0.93	1.11	0.84
	Peak hepatic SUV (NASH)	0.76	0.93	0.82
Rosuvastatin	Systemic exposure (AUC_{0-inf})	0.85	0.81	1.05
	Peak concentration (C_{max})	0.80	0.83	0.96

SUV: standardized uptake values

CONCLUSIONS

- A virtual NAFLD population model within the PBPK framework was successfully developed with a good predictive capability of estimating disease-related changes in drug PK
- The verified model may help inform dose adjustment of drugs commonly used to treat comorbidities in this patient population
- This also supports the use of model-informed predictions of the PK of new or repurposed drugs for potential treatment of NAFLD

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