

Semi-mechanistic model to characterize effects of gastric emptying on glucose absorption profiles in obese and non-obese adults

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Background

- Recent studies indicate that obesity is altering gastric emptying and glucose absorption
- Interactions between altered gastric emptying, glucose absorption and glycemic control in obese subjects are not well understood
- It is clinically relevant to characterize and compare effects of gastric emptying on glucose absorption profiles and glycemic control in obese and non-obese subjects

Objectives

Characterize and compare effects of gastric emptying on glucose absorption and glycemic control in obese and non-obese healthy adults.

Methods

Experimental Data

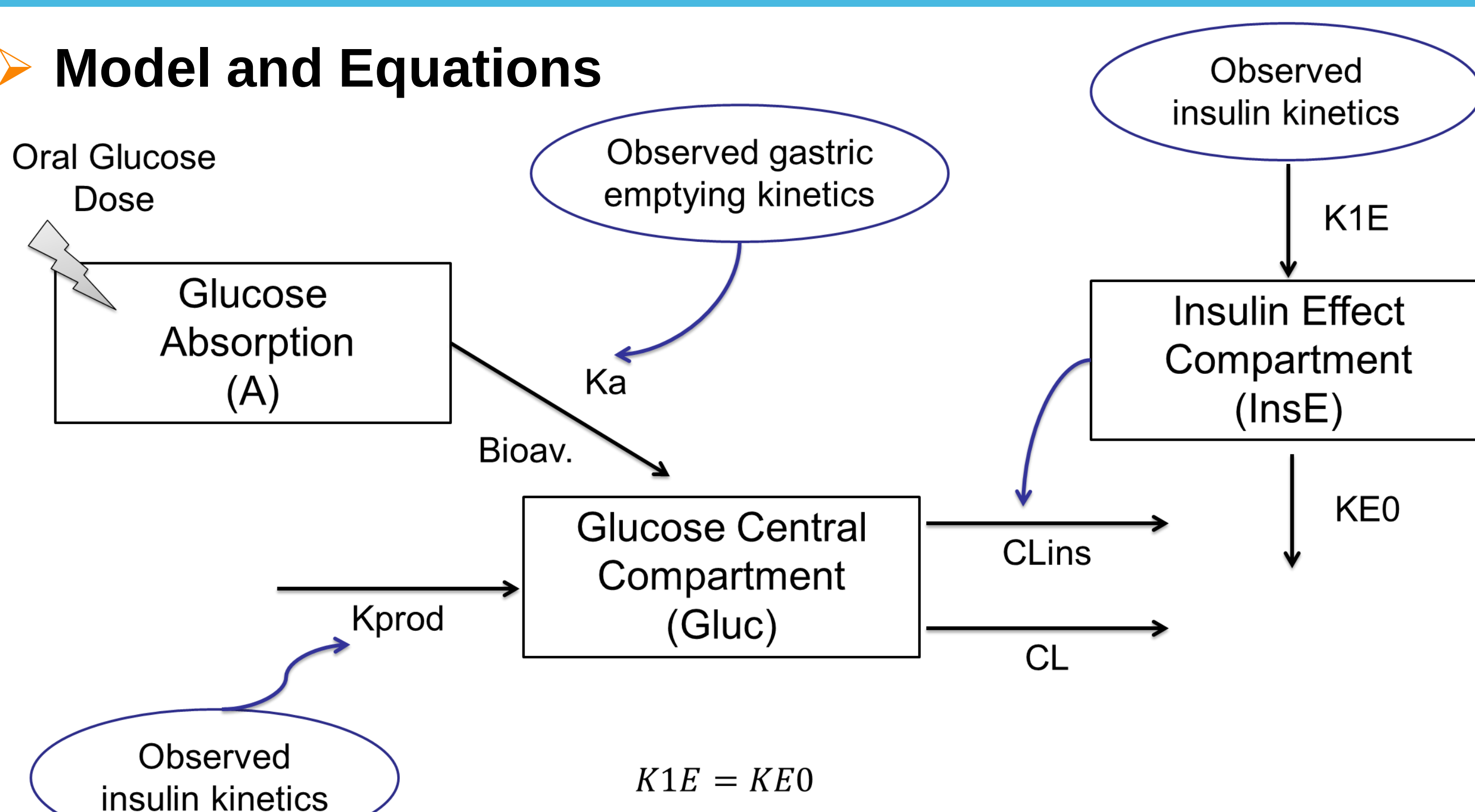
- Oral Glucose Tolerance Tests (OGTTs):** 60 healthy adults received a solution containing 10g, 25g or 75g of glucose
- Glucose, insulin, incretin (gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)) and gastric emptying data available in:
 - 24 non-obese healthy adults
 - 36 obese, otherwise healthy adults

Model Building

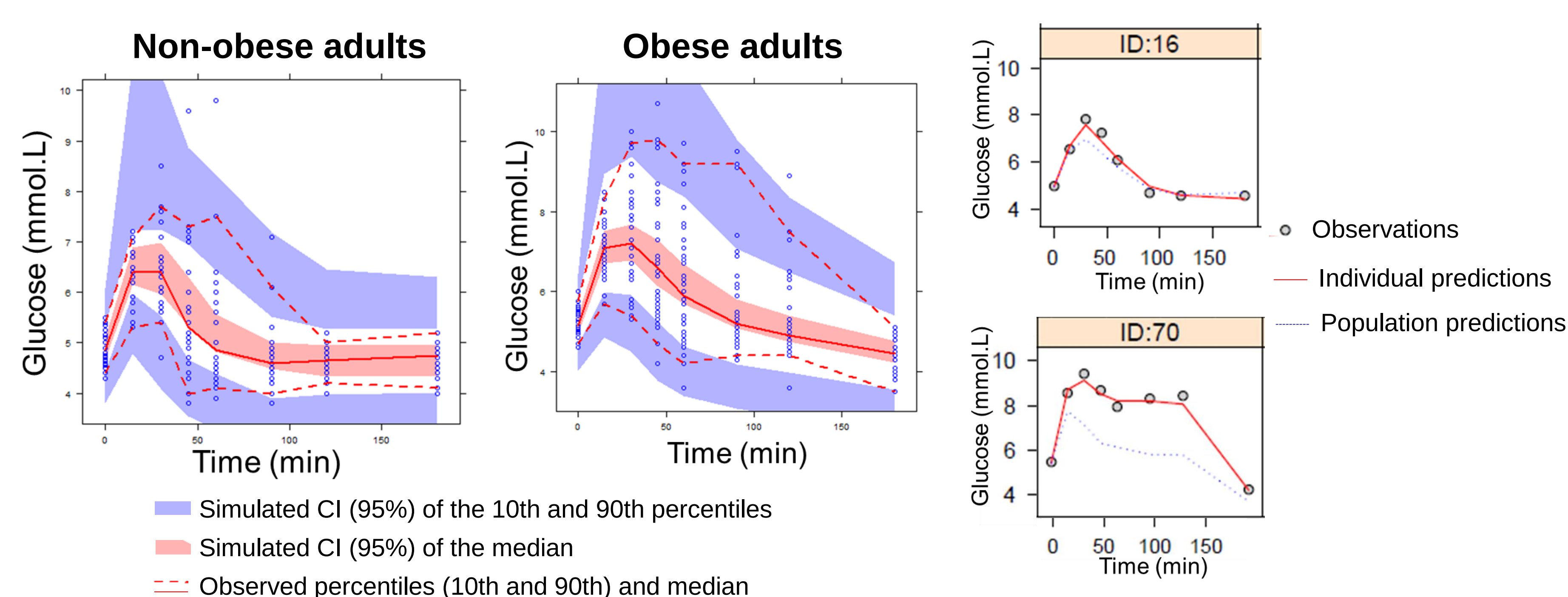
- Semi-mechanistic model** characterizing gastric emptying effects on glucose absorption and glycemic control
- Population analysis** with non-linear mixed effects modeling approach using NONMEM 7.3
- Model selection and evaluation: criteria based on the likelihood, goodness-of-fit plots and simulation-based diagnostic (VPC)

Results

Model and Equations



Model Evaluation: VPCs and Individual fits



Non-obese healthy adults:

$$\frac{dA}{dt} = -Ka \times A$$

$$\frac{dGluc}{dt} = Kprod \times \left(\frac{Ins}{Ins0}\right)^{POW} + Ka \times A - \left(CL \times \frac{Gluc}{Vd} + CLI \times \frac{Gluc}{Vd} \times InsE \right)$$

$$\frac{dInsE}{dt} = InsE \times K1E - KE0 \times InsE$$

Obese healthy adults:

$$\frac{dA}{dt} = -Ka \times A$$

$$\frac{dGluc}{dt} = Kprod \times \left(\frac{Ins}{Ins0}\right)^{POW} + Ka \times A - \left(CL \times \frac{Gluc}{Vd} + \frac{Gluc}{Vd} \times \frac{CLImax \times InsE^H}{INS50^H + InsE^H} \right)$$

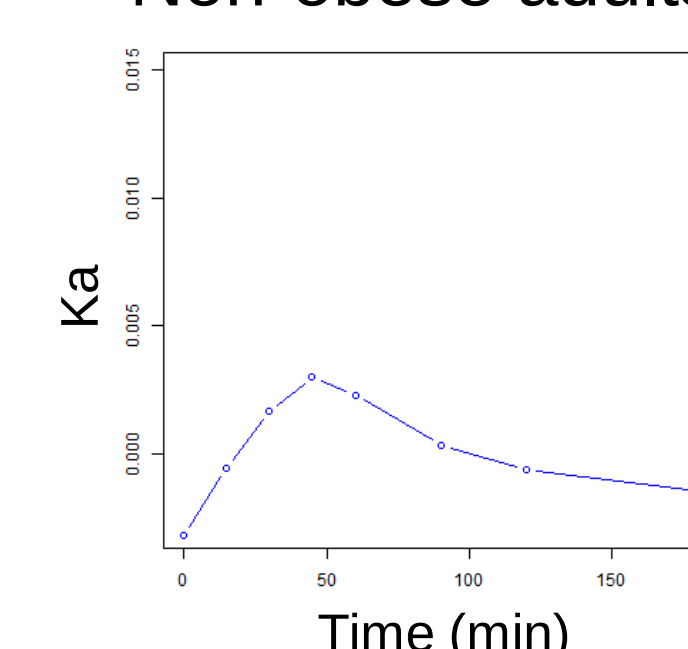
$$\frac{dInsE}{dt} = InsE \times K1E - KE0 \times InsE$$

Differences between obese and non-obese healthy adults

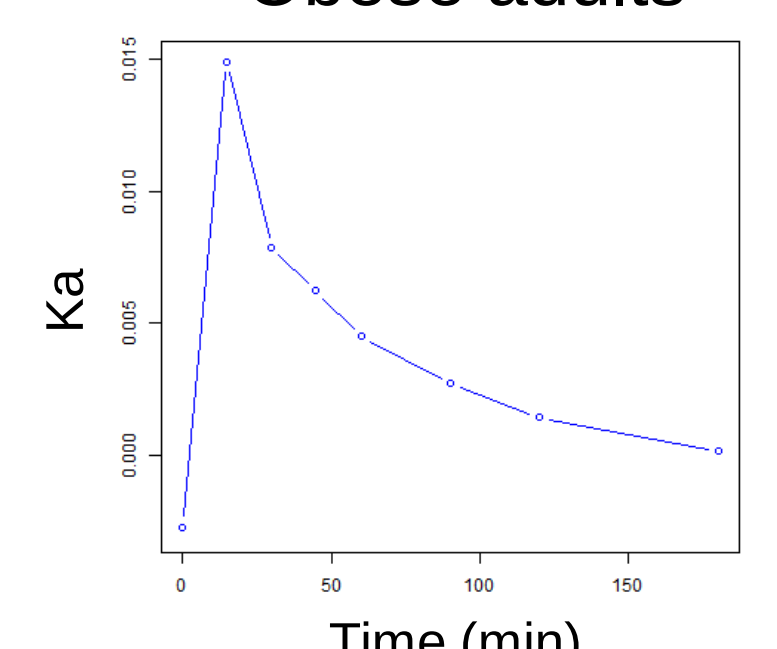
Parameter	Obese	Non obese
Absorption rate: Ka (day ⁻¹)	0.003	0.0004
Production rate: Kprod (mmol.L ⁻¹ . day ⁻¹)	0.3	0.8
Clearance insulin-independent: CL (day ⁻¹)	0.06	0.1
Insulin effect on clearance	Saturable effect	Linear effect

Time-dependent glucose absorption rate:

Non-obese adults



Obese adults



Conclusions

- First semi-mechanistic model characterizing interactions between gastric emptying, glucose absorption and glycemic control in obese and non-obese healthy adults
- Such model can be applied to investigate effects of bariatric surgery on glucose kinetics and characterize differences in glucose absorption between adults and pediatrics with or without obesity and/or diabetes mellitus