# Linking 4GI Glucose Homeostasis and Hall Body Composition Models to study GLP-1R agonist effects on glucose and body weight

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## Introduction

- Our previously published 4GI systems pharmacology model describes drug effects on glucose (GLC), glucagon-like peptide-1 (GLP-1), glucagon (GLG), glucose-dependent insulinotropic peptide (GIP) and insulin (INS) (4GI) dynamics in type 2 diabetes mellitus (T2DM) and healthy volunteers (HV) [1].
- However, body weight effects on insulin sensitivity were not captured.
- The Hall body composition model describes the physiology of metabolism, fuel selection, and body composition changes in humans [2].

## Objectives

- This investigation aimed to link the 4GI [1] with the Hall body composition model [2] to quantify the effect of GLP-1 receptor (GLP-1R) agonists on body weight, and body weight effects on glucose homeostasis.

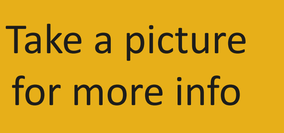
## Methods

- A literature dataset was created including body composition, energy expenditure (EE) and GLC related data (Table 1).
- In the combined 4GI-Hall model only diet and food related parameters, and body weight effect on insulin dependent glucose clearance (Clglci) were estimated, all other system parameters were kept fixed.
- In the Hall part of the model, the diet effect ($Diet_{eff}$) on energy intake (EI) was modelled as an initial decline in food intake, followed by a decrease of the effect over time.
- The GLP-1R agonistic effect on EI was described with an $E_{MAX}$ relation, driven by the *in vitro* $EC_{50}$ normalized drug concentration.
- The *in vivo* $EC_{50}$ of the GLP-1 effect (GLP50) on EI was estimated, including a time dependent increase in the $EC_{50}$ to model the tolerance of the effect.
- The Hall model-predicted absolute change from baseline body weight (WTCH) was modelled as a continuous covariate on the 4GI CLglci parameter.

## Capturing the effect of weight loss on insulin sensitivity

### diet

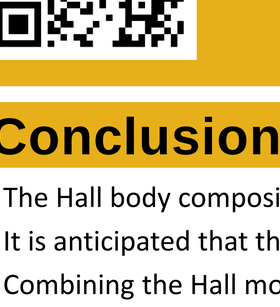
$$Diet_{effect} = 1 - DIETI * K_{diet} * \frac{(e^{-K_{diet}*t} - e^{-K_{red}*t})}{K_{red} - K_{diet}}$$



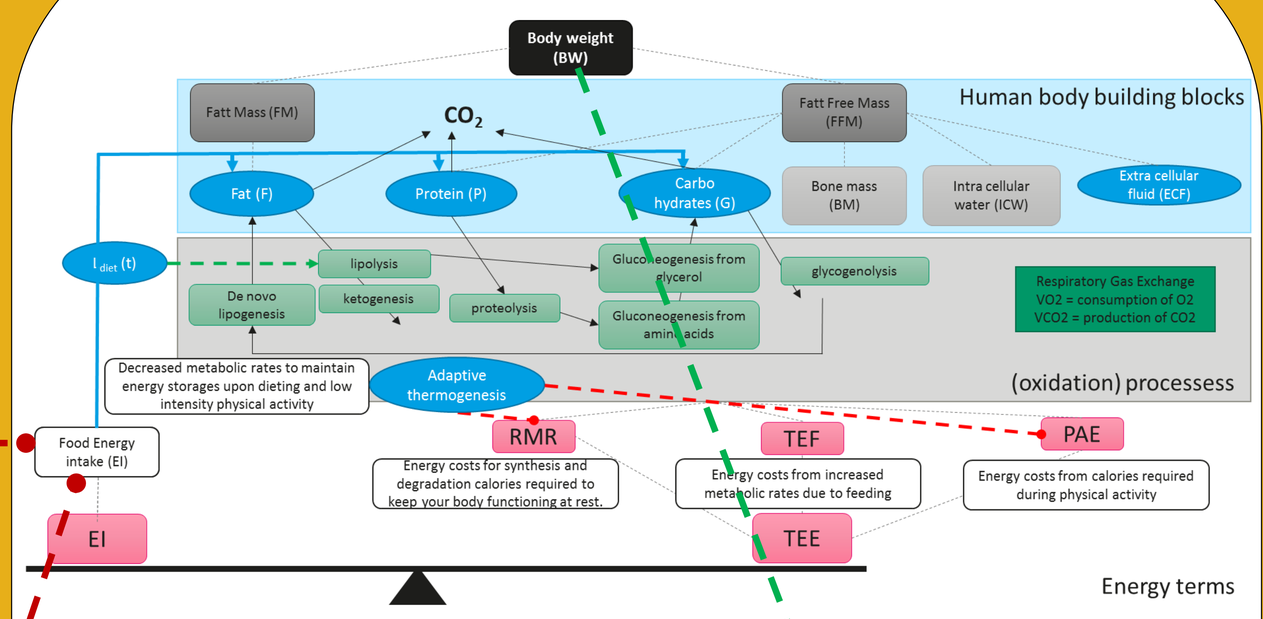

### GLP-1R agonist

$$GLP_{effect} = 1 - EMAX * \frac{\frac{C_{drug,free}}{EC_{50,drug,in\ vitro}}}{GLP50 + \frac{C_{drug,free}}{EC_{50,drug,in\ vitro}}}$$

$$GLP50 = TVGLP50 + \frac{SSEC50 * TAFD}{T50 + TAFD}$$



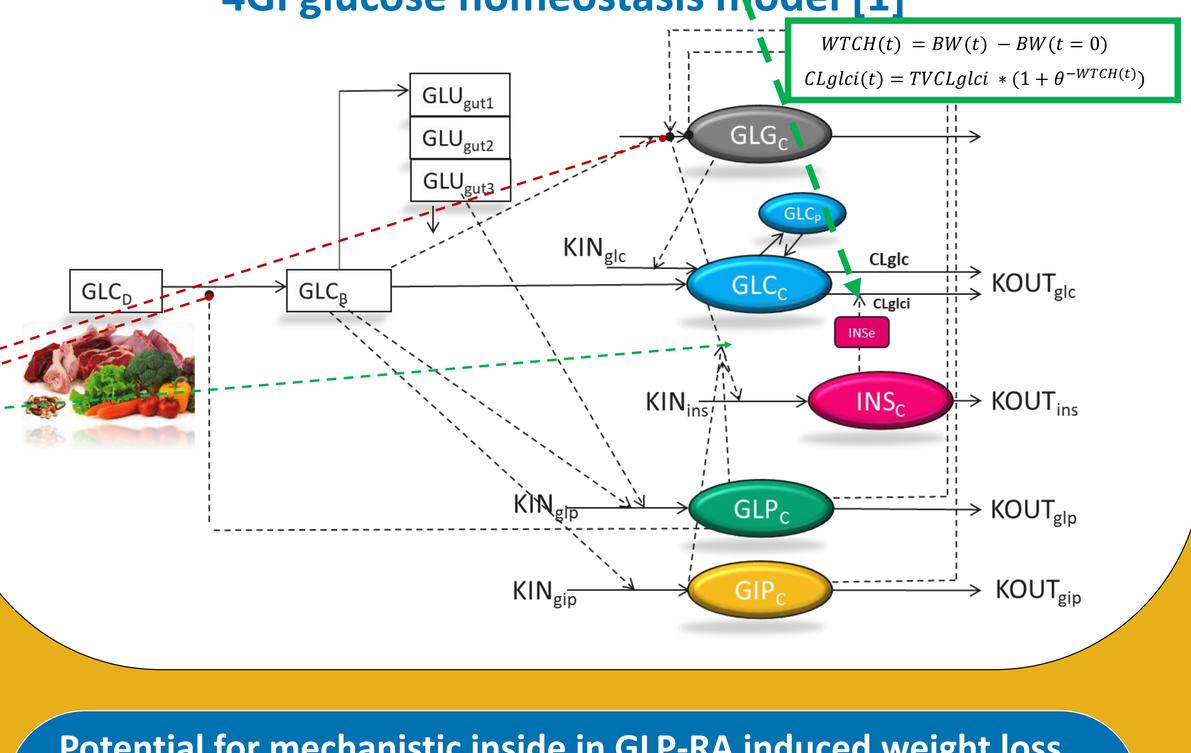

### Hall body composition model [2]




### 4GI glucose homeostasis model [1]

$$WTCH(t) = BW(t) - BW(t=0)$$

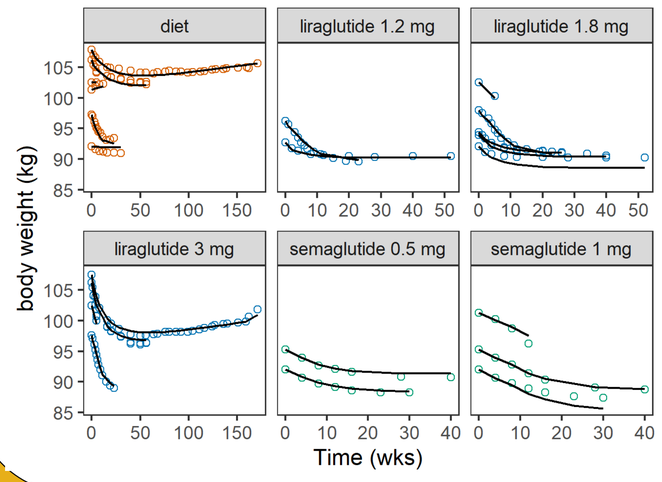
$$CLglci(t) = TVCLglci * (1 + \theta^{-WTCH(t)})$$



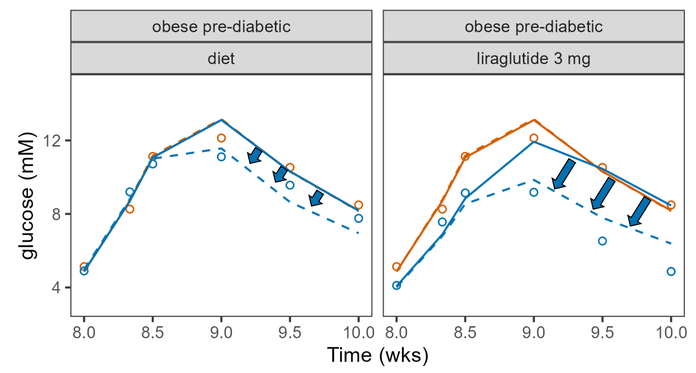

### Table 1: Data included

| Original Paper | Part original model development | Study type | Population |
|---|---|---|---|
| 10 publications | 4GI | Various challenges to glucose system | Healthy/Type 2 diabetic |
| LEAD-3/LEAD-6/AWARD-6 | 4GI | Liraglutide clinical studies | Type 2 diabetic |
| Heilbronn 2006 | Hall | CALERIE study | Healthy |
| Redman 2007 | Hall | CALERIE study | Healthy |
| Redman 2009 | Hall | CALERIE study | Healthy |
| Racette 2011 | | CALERIE study | Healthy |
| Das 2017 | | CALERIE study | Healthy |
| Guo 2018 | | CALERIE study | Healthy |
| Schrauwen 1997 | Hall | Diet study | Healthy |
| Smith 2000 | Hall | Diet study | Healthy |
| Jebb 1993 | Hall | Diet study | Healthy |
| Jebb 1996 | Hall | Diet study | Healthy |
| Rumpler 1991 | Hall | Diet study | Healthy Obese |
| de Boer 1986 | Hall | Diet study | Healthy Obese |
| Diaz 1992 | Hall | Diet study | Healthy |
| Svetkey 2008 | Hall | Diet study | Healthy |
| Weiss 2015 | | Calorie restriction and exercise study | Healty Obese |
| Can 2014 | | Liraglutide clinical study | Healthy Obese |
| Halawi 2017 | | Liraglutide clinical study | Healthy Obese |
| le Roux 2017 | | Liraglutide SCALE study | Healthy or Pre-diabetic Obese |
| Pi-Sunyer 2015 | | Liraglutide SCALE study | Healthy or Pre-diabetic Obese |
| Blundell 2017 | | Semaglutide NCT02079870 study | Healthy Obese |
| Hjerpsted 2017 | | Semaglutide NCT02079870 study | Healthy Obese |
| Sorli 2017 | | Semaglutide SUSTAIN 1 study | T2DM |
| Pratley 2018 | | Semaglutide SUSTAIN 7 study | T2DM |

### Adequate description of the effect of diet and GLP-1R agonists on body weight

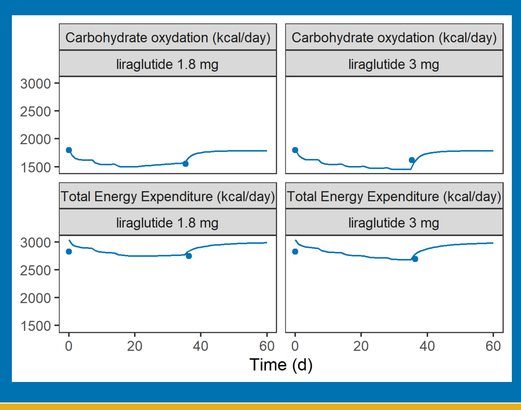



### Improved glucose description with weight loss effect on insulin sensitivity




Take a picture for more info

### Potential for mechanistic inside in GLP-RA induced weight loss




- Model is able to describe trends in underlying biomarkers
- Potential for more insight in the underlying mechanisms involved

## Conclusions

- The Hall body composition model was successfully extended for GLP-1R agonistic effects on body weight by assuming an inhibiting effect on energy intake.
- It is anticipated that the GLP-1R agonist extended Hall model can also be applied for new compounds due to the use of *in vitro* $EC_{50}$ normalized free drug concentration as driver of the GLP-1 effect.
- Combining the Hall model with the 4GI model showed that weight loss has a positive effect on insulin sensitivity.
- The slope of the linear covariate effect relationship between weight loss and CLglci was estimated to be 0.13 kg-1, indicating that a weight loss of 1 kg results in a 13% increase in CLglci.
- The combined model was able to describe trends in underlying biomarkers.
- Further integration of the models could potentially increase mechanistic insight and answer mechanism of action related questions of GLP-1R agonists and related compounds.

**[1] Bosch, R., Petrone, M., Arends, R., Vicini, P., Sijbrands, E.., Hoefman, S., Snelder, N. (2022). A novel integrated QSP model of in vivo human glucose regulation to support the development of a glucagon/GLP-1 dual agonist. CPT:PSP, 11(3), 302–317.**
**[2] Hall, K. D. (2010). Predicting metabolic adaptation, body weight change, and energy intake in humans. American Journal of Physiology - Endocrinology and Metabolism, 298(3).**