

An integrated Model for Glucose and Insulin Regulation in Bariatric Surgery Patients following Intravenous Glucose Tolerance Test

Background

- Obesity is associated with insulin resistance, while weight loss is closely correlated with increasing insulin sensitivity (1)
- Gastric Bypass Surgery (GBS), currently the most effective way of sustained weight loss, is associated with improved β -cell function and glucose control by reducing insulin resistance (2,3)
- Exercise has shown to be effective at improving glucose control in GBS patients (4)
- Intravenous glucose tolerance test (IVGTT) is an established method to measure insulin resistance (5)
- To our knowledge, changes in glucose metabolism after GBS have not been quantitatively described by an integrated glucose-insulin model following IVGTT

Objectives

- To **develop** an IVGTT model to describe glucose and insulin interplay in GBS patients
- To **investigate** differences in glucose control and insulin resistance in patients following a 6-month exercise intervention compared to a control group
- To **evaluate** possible covariates that explain differences between exercise and control group in their glucose insulin interplay following IVGTT

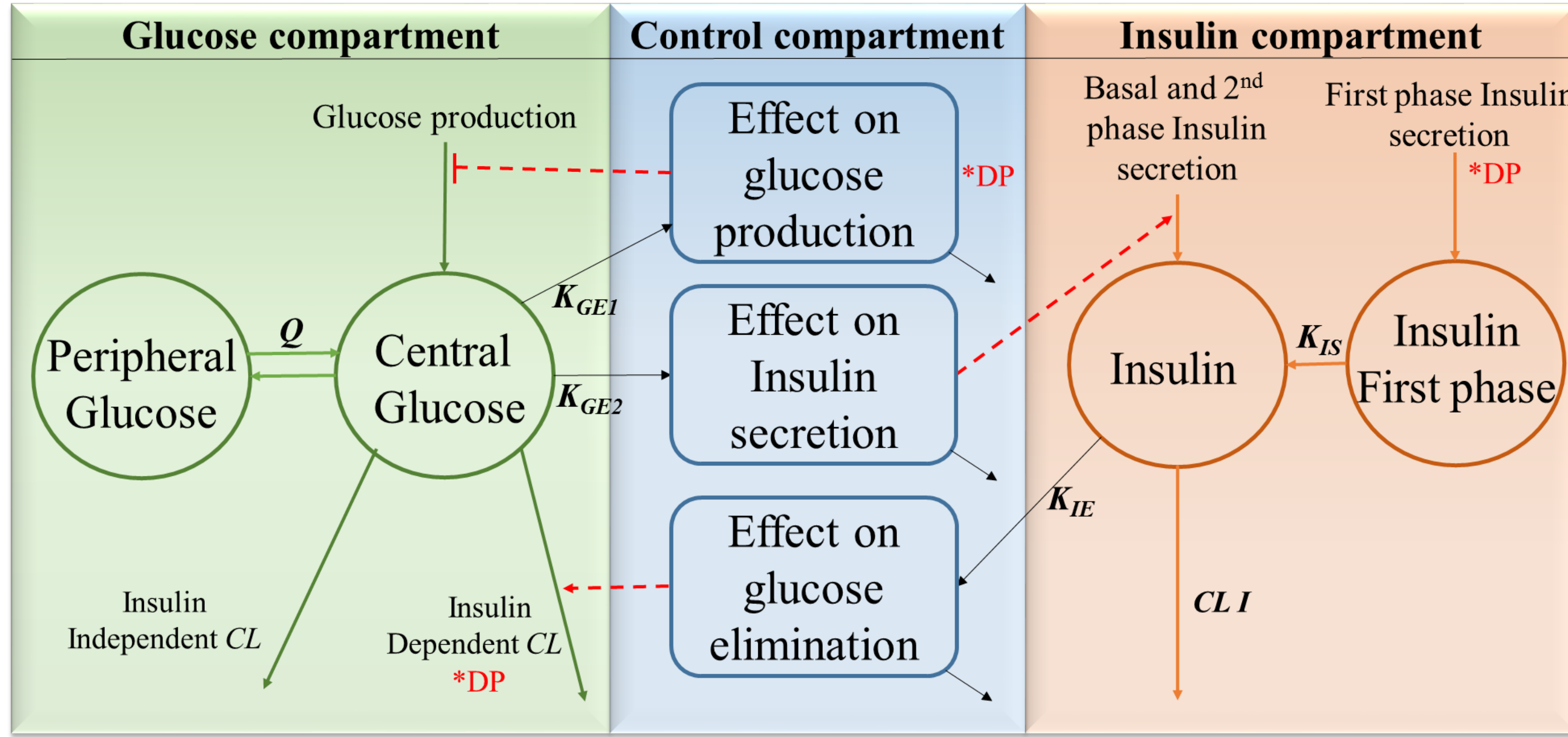


Figure 2: Schematic overview of the IVGTT model

Methods

Subjects

Mean and range of clinical trial data from 119 GBS patients (4) (Figure 1):

- Exercise group (n= 60):**
 BMI 38.3 [28.9 - 61.3] kg/m²,
 Weight 108.4 [75.4 - 196.7] kg,
 Age 38.3 [21 - 60] years
- Control group (n= 59):**
 BMI 38.7 [26.9 - 55.9] kg/m²
 Weight 106.2 [69.2 - 109.2] kg, Age 38.7 [22 - 61] years

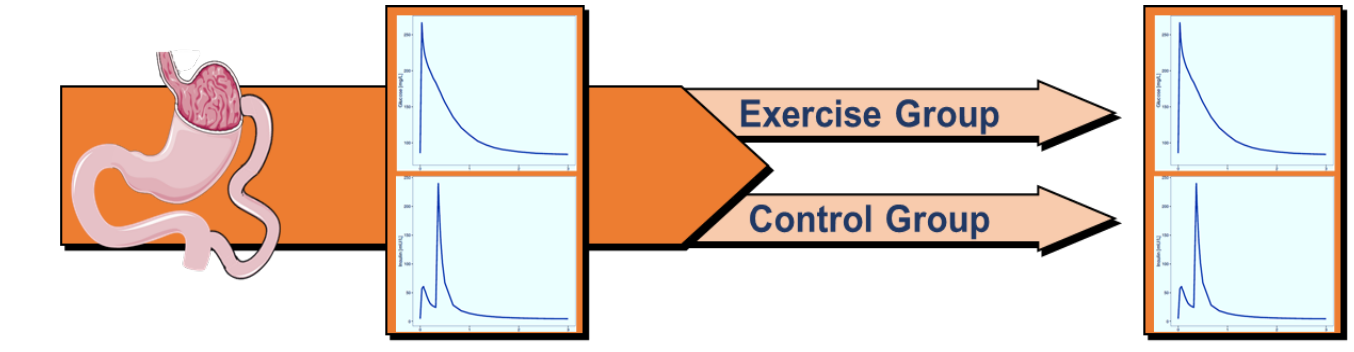


Figure 1: Study design overview

Intervention

- IVGTT was conducted 3 months after GBS, and repeated after a six month intervention period.
- randomized controlled physical activity intervention (using treadmills, stationary bikes, rowing machine, or walking track) was defined as a minimum of three and maximum of five exercise sessions per week
- Blood samples** were obtained at 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min following an IV bolus dose of 12g/m² Glucose. 19 min after start of glucose injection, an Insulin dose of 1.5 units/ 12g/m² was given.

IVGTT Model

- An IVGTT model was developed in NONMEM[®]7.3 using the model formulated by Silber *et al.* (6) as a starting point.
- Linear **disease progression** (DP) was included to investigate the impact of exercise *versus* non-exercise intervention. DP was tested on various parameters to **evaluate and compare differences in glucose and insulin regulation** between the **control** and the **exercise group post GBS**. (Figure 2)
- Waist circumference (waist), total abdominal fat (TFATAB), and treatment group (TMG) were tested as covariates (COV).on model parameters

$$TVPAR = (1 + \theta * (COV - median(COV))) * TVPAR_0$$

$$TVPAR = \theta \cdot TVPAR_0 \quad \theta = \theta_{exc}(Exc\ Visit: 2) \ \& \ \theta = 1 \ (otherwise)$$

Results

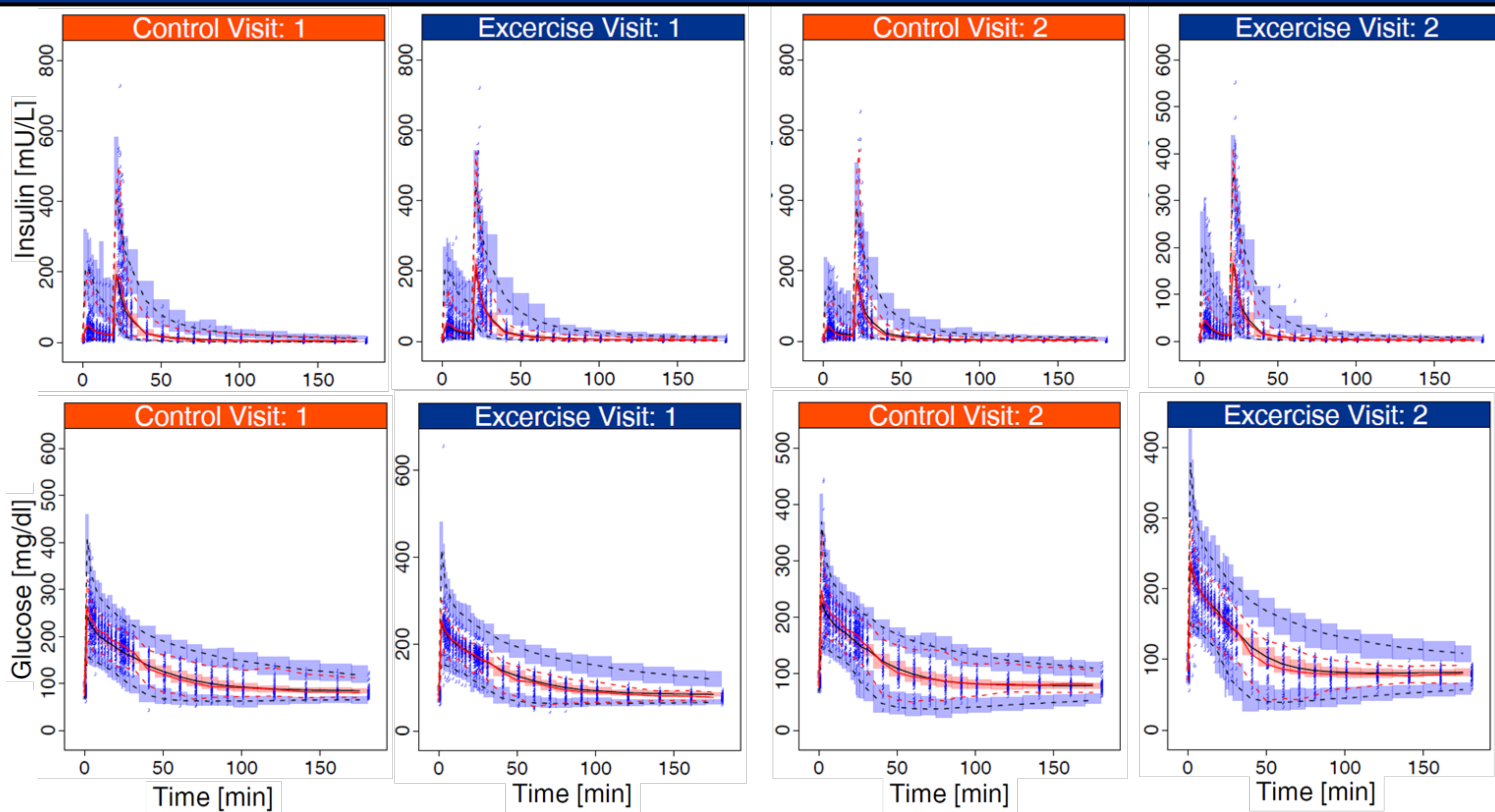


Figure 3: Prediction corrected visual predictive checks (VPCs). Solid lines represent median and dashed lines the 5th and 95th percentiles. The red lines represent observations and black lines the simulated data from the model. The shaded areas represent 95% confidence intervals for the simulated median, 5th and 95th percentile

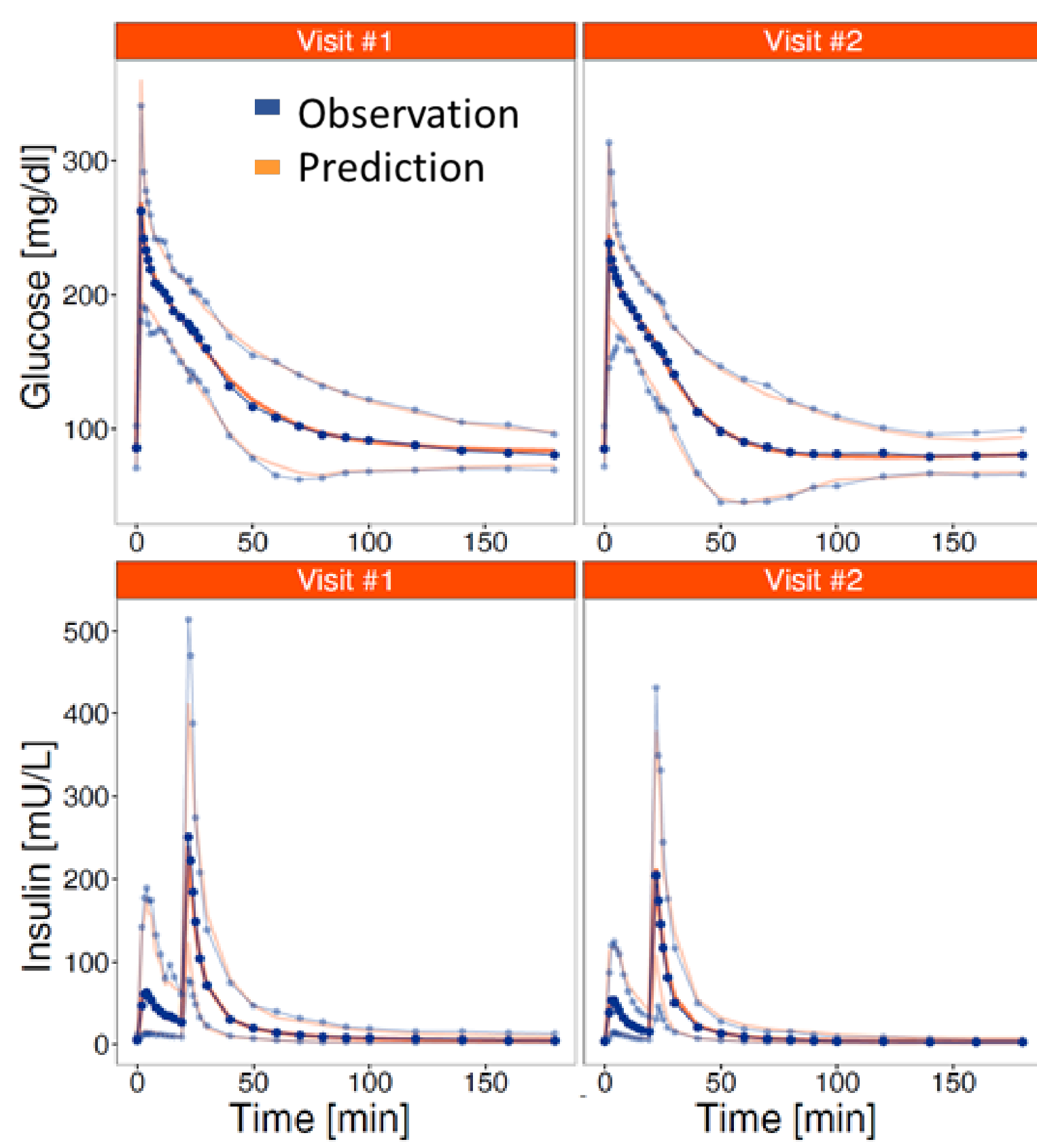


Figure 4: Mean predictions and observations

- The developed model predicts the observed data well, as shown in the plots in Figure 3 and Figure 4
- Linear DP was implemented on the negative feedback of glucose production (GPRG), insulin stimulated glucose uptake (CLGI), and insulin first phase secretion (IFPS)
- CLGI**, key player in this model linked to insulin resistance showed a **25.7% higher improvement in the exercise group** as compared to the control group (Figure 5A)
- GPRG **increased by 71% in the control group** after the 6 months intervention, as compared to 54.5% in the exercise group (Figure 5B), showing an improved ability of the exercise group to maintain a healthy state better
- IFPS **decreased** within the 6 months intervention, with a smaller effect on the exercise group (-1.79%) as compared to the control group (-25.5%) (Figure 5C)
- Waist, TFATAB, and TMG were added as COV to explain differences in glucose control and insulin resistance between exercise and non-exercise intervention

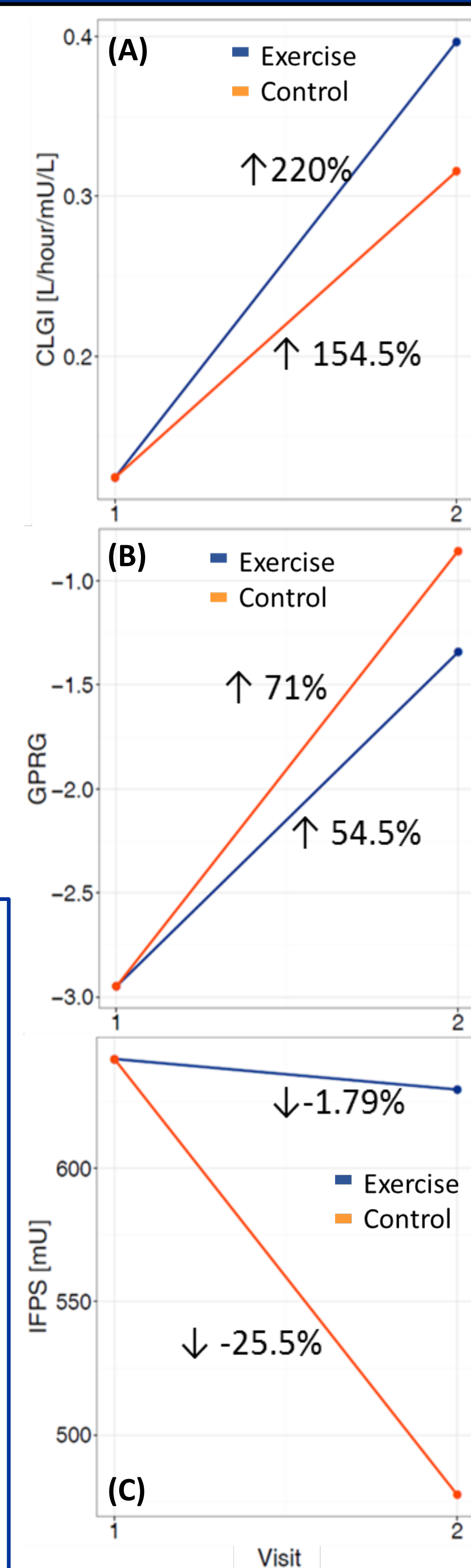


Figure 5: Disease progression of IVGTT on model parameter (A) CLGI, (B) GPRG, and (C) IFPS

Parameter	Estimates		IIV[%]
	Control Group	Exercise Group	
KGE1 [1/hr]	7.35	108.6	
KGE2 [1/hr]	4.54	54.5	
KIS [1/hr]	28.90	44.5	
KIE [L/hr]	1.02	98.9	
CLG [L/hr]	7.08	72.3	
CLGI [L/hour/mU/L]	0.12	79.1	
after intervention CLGI [L/hour/mU/L]	0.32	0.40	
CLI [L/hr]	102.00	56.4	
GSS [mg/dl]	82.80	9.9	
ISS [mU/L]	4.12	45.7	
IFPS [mU]	641.00	97.9	
after intervention IFPS [mU]	477.55	629.53	
VGC [L]	10.30	59.5	
VI [L]	8.97	48.6	
VGP [L]	7.23	21.8	
Q [L/hr]	155.00	107.7	
GPRG	-2.95	93.5	
after intervention GPRG	-0.86	-1.34	
IPRG	1.91	39.1	
prop. error glucose [%]	5.92		
prop. error insulin [%]	28.40		

COVARIATES	
TFATAB on KGE1	-0.0013
TMG on KGE2	0.46
TMG on CLI	1.01
TMG on GSS	1.04
TMG on ISS	0.76
Waist on Q	0.0066
TMG on IPRG	0.93

Table 2: Final parameter estimates

Conclusions

- The **semi-mechanistic** model presented was able to describe the glucose and insulin profile following an IVGTT adequately well
- Exercise has been shown to be beneficial as compared to non-exercise intervention after GBS for glucose control and insulin sensitivity
- Insulin stimulated **glucose uptake**, the key player for insulin resistance, **increased** after 6 months intervention, in exercise even more than in the control group
- Further COV from energy expenditure will be tested to explain the inter individual variability (IIV), once available

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