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 interplay following IVGTT.

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 103.4 (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.

**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, and 180 min following an IV bolus dose of 12g/kg Glucose. 19 min after start of glucose injection, an insulin dose of 1.5 units/12g/kg 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.
- Continuous COV:
  - **TVPAR = (1 + θ × (COV − median(COV))) × TVPAR₀**
  - Categorical COV:
    - **TVPAR = θ × TVPAR₀**
      - θ = 1 (otherwise)

Results

- 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, TATAB, and TMG were added as COV to explain differences in glucose control and insulin resistance between exercise and non-exercise intervention.

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 (IVIV), once available.