

Comparison of post-prandial glucose control by two GLP-1 receptor agonists (lixisenatide and liraglutide) in type 2 diabetes

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ABSTRACT

Background and aims: The aim of this study was to develop mechanistic models for lixisenatide, a short-acting GLP-1 receptor agonist, and liraglutide, a long-acting one, in order to compare their mechanisms of action and the relative contributions of their respective effect sites to their overall post-prandial glycaemia control. The integrated glucose-insulin (IGI) model¹ has previously been used to quantify the contribution of various pathways on the overall mechanism of action of antidiabetic compounds². In order to account for all effect sites of lixisenatide and liraglutide, the IGI model was extended with a glucagon-component.

Data and methods: Glucose, insulin and glucagon data during glucose provocation experiments (one IVGTT and two meal test studies) were analysed. A K-PD analysis³ of the test drug's effects on selected parameters (insulin secretion, gastric emptying, hepatic glucose output, glucagon production and insulin sensitivity) was performed.

Results: The IGI+glucagon (IGIG) model was able to adequately describe glucagon profiles in type 2 diabetic patients. The drug-effect model structures for lixisenatide and liraglutide were similar: identified mechanisms of action included suppression of glucagon production and increase of insulin secretion, gastric emptying time and insulin sensitivity.

Simulations show that the increase of insulin secretion is the most important factor for lowering plasma glucose by liraglutide. For lixisenatide, the gastric emptying effect is most influential during the meal test. The glucagon-mediated effect on post-prandial glycaemic control was not substantial despite both compounds having a significant effect on glucagon production.

INTRODUCTION

Background

- Lixisenatide is a once daily short-acting, prandial GLP-1 receptor agonist (GLP-1RA) shown to be associated with significant improvements in glycaemic control with good tolerability in people with Type 2 diabetes mellitus (T2DM)⁴.
 - A comparison of lixisenatide's postprandial effects with those achieved by the longer-acting GLP-1 agonist liraglutide (Victoza®) was considered of interest.
 - Both compounds' action on glucagon concentration-time profiles were of particular research interest.
- Objectives**
- To extend the IGI model with a glucagon component, capturing its most important interactions with the glucose-insulin system (glucose and insulin effects on glucagon production, glucagon effect on endogenous glucose production and meal effect on glucagon production) and following both intravenous and oral glucose stimulation experiments (IVGTTs and meal tests).
 - To better characterise lixisenatide's and liraglutide's mechanisms of action and to quantitatively compare the relative contributions of their multiple effect sites to their overall effect on post-prandial glycaemic control.

DATA AND METHODS

Lixisenatide studies in type 2 diabetic patients

- Single-dose IVGTT study (only placebo data used – PDY10433 (NCT00931372))
- 13-week dose ranging study, meal tests at baseline and end of study – DRI6012 (NCT00299871)
- 4-week head-to-head comparison with liraglutide, meal tests at baseline and end of study - PDY10931 (NCT01175473)
- Details in Table 1

Study	Duration	No. of patients	Dose(s)	Comparator	FPG	Body weight
IVGTT	Single dose	21	20 µg	Placebo	109.7 ± 12.3	88.8 ± 9.0
Ph IIb dose ranging	13 weeks	230	5-30 µg QD and BID	Placebo	165.4 ± 38.0	92.3 ± 15.4
Comparison to liraglutide	4 weeks	143	20 µg	Liraglutide 1.8 mg	159.8 ± 29.5	91.9 ± 15.9

Table 1. Study design and population

Modelling analysis

- A glucagon compartment was added and its most important interactions with glucose and insulin (glucose and insulin effects on glucagon production, glucagon effect on endogenous glucose production and meal effect on glucagon production) were incorporated (Figure 1).
- Compared to the glucagon model published by Schneek et al⁵, this new model utilises fewer compartments, with improved goodness-of-fit diagnostics.
- A K-PD analysis of the test drug's effects on selected parameters (insulin secretion, gastric emptying, hepatic glucose output, glucagon production and insulin sensitivity) was performed. Sites of drug action were added one at a time. The best effect site was selected and all other sites were tested again until no further improvement of fit could be obtained by adding further effect sites.
- Simulations were performed to separately investigate the contribution of each effect site.

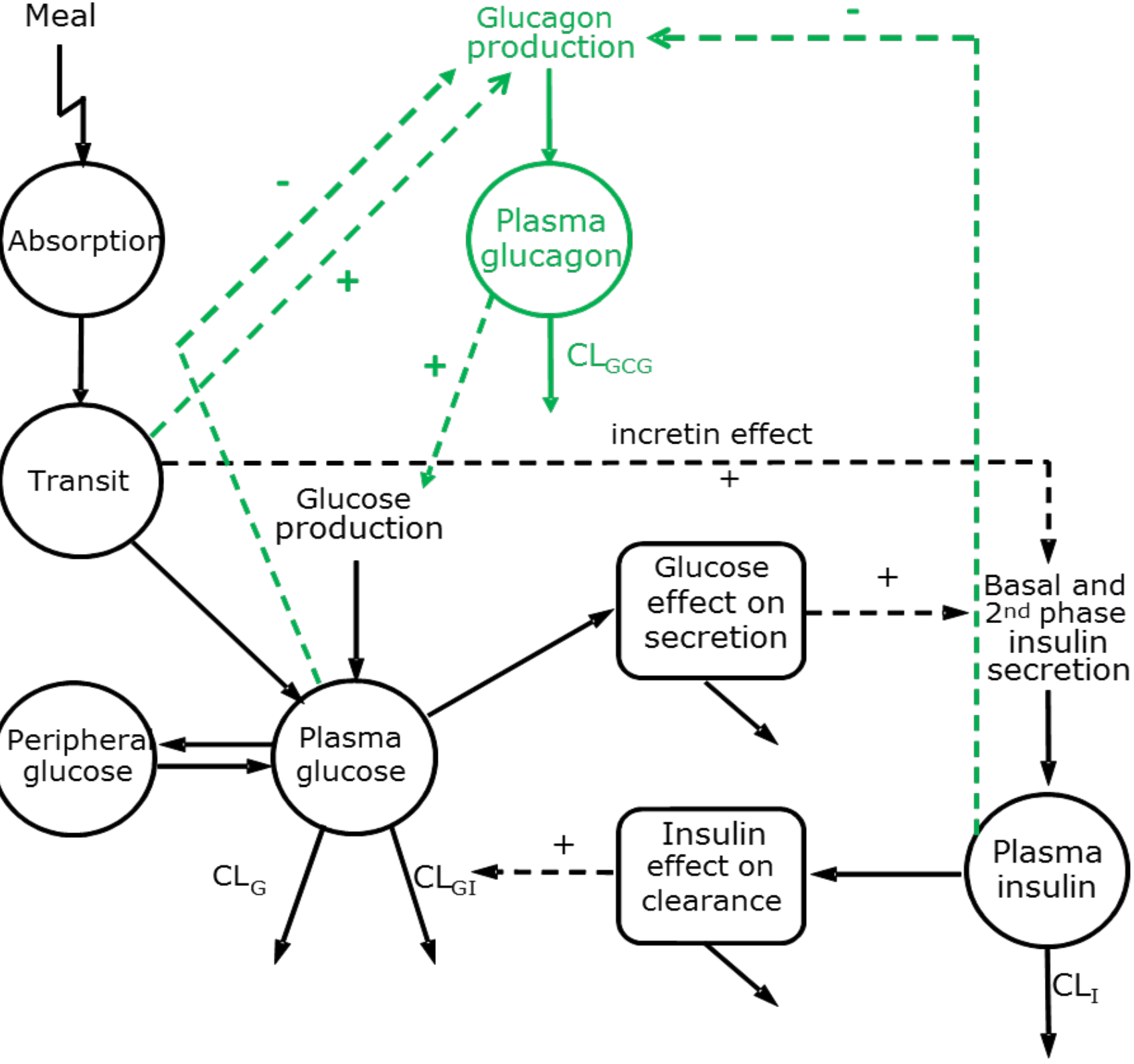


Figure 1. Model outline. Glucagon part in green. CL_G: insulin-independent glucose clearance, CL_{GI}: insulin-dependent glucose clearance, CL_I: insulin clearance, CL_{GCG}: glucagon clearance.

RESULTS

Glucagon profiles

- The updated model was able to adequately describe glucagon profiles both following IVGTTs and meal tests (Figures 2 and 3), despite very different behaviour (drop after IVGTT, rise after meal).

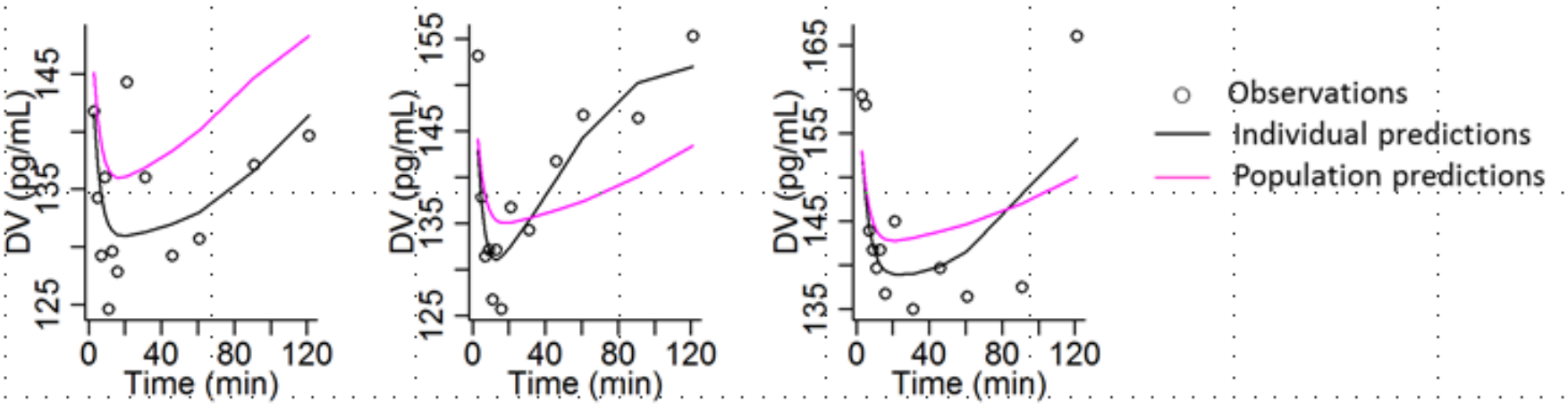


Figure 2. Individual glucagon concentration-time profiles following IVGTT (placebo)

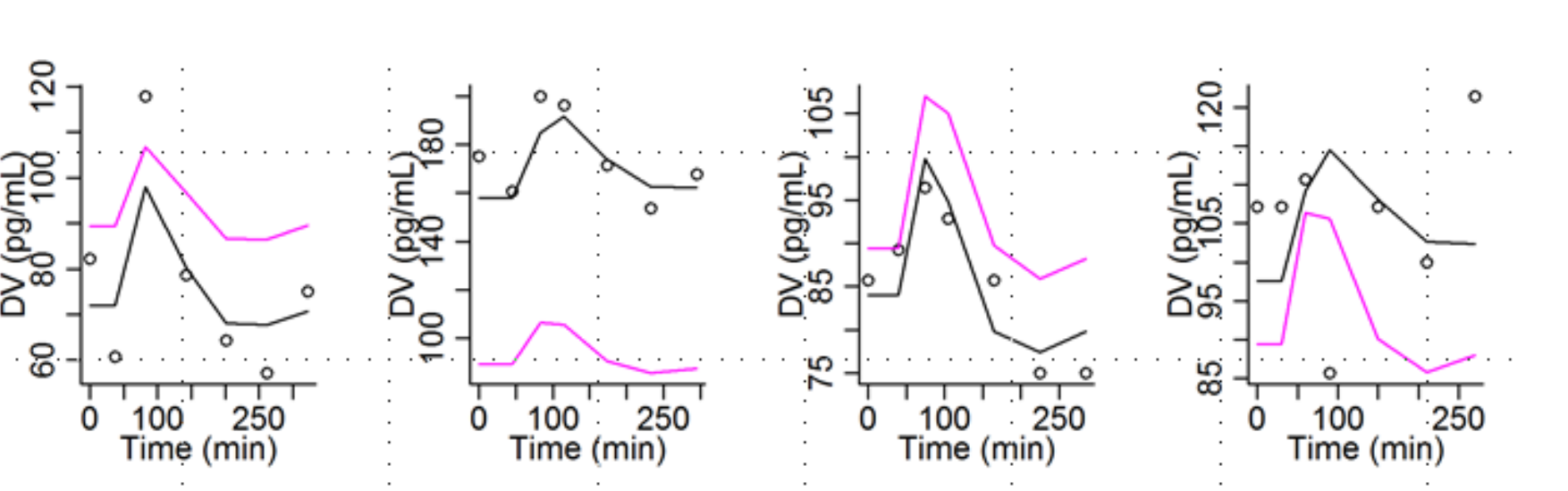


Figure 3. Individual glucagon concentration-time profiles following meal test (placebo)

Lixisenatide's glycaemic effects

- Adequate fit for glucose, insulin and glucagon profiles (Figure 4)
- Four sites of action determined:
 - Increased insulin secretion
 - Delayed gastric emptying
 - Reduced glucagon production
 - Increased insulin sensitivity
- Some effects are time-dependent: inhibition of glucagon production, gastric emptying (almost completely blocked in the first few hours after drug intake), part of the increase in insulin secretion (see Figure 6)
- Other effects are constant throughout the observation window (4.5 hours post meal test): increased insulin sensitivity, part of the increase in insulin secretion
- Gastric emptying effect most prominent

Liraglutide's glycaemic effects

- Adequate fit for glucose, insulin and glucagon profiles (Figure 5)
- Same sites of action determined, but their relative importance is different
- Increased insulin secretion most important
- All drug effects constant throughout the observation period (probably due to longer half-life than lixisenatide)

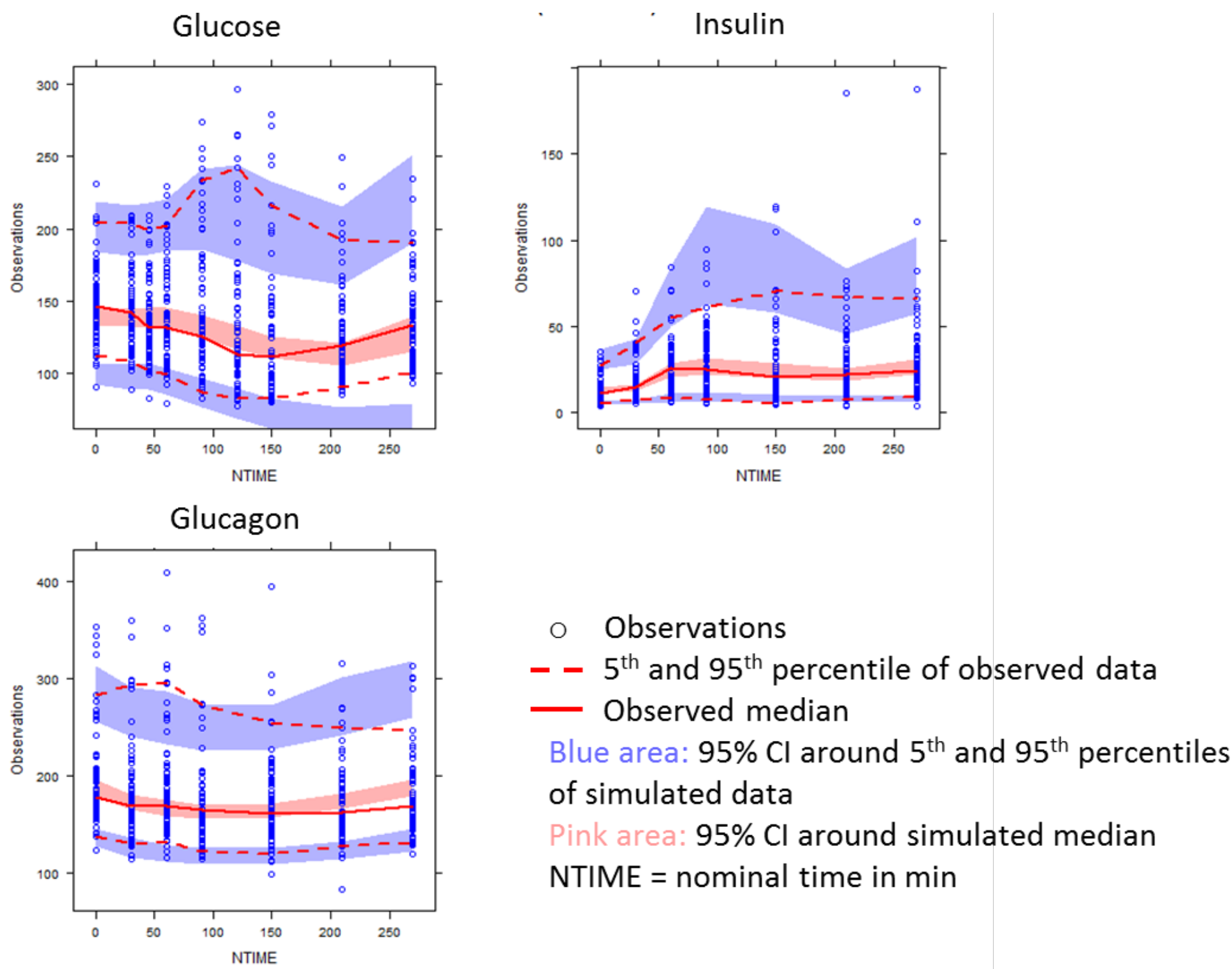


Figure 4. Visual predictive check (VPC): glucose, insulin and glucagon profiles at study week 4 following a standardised breakfast (lixisenatide 20 µg arm).

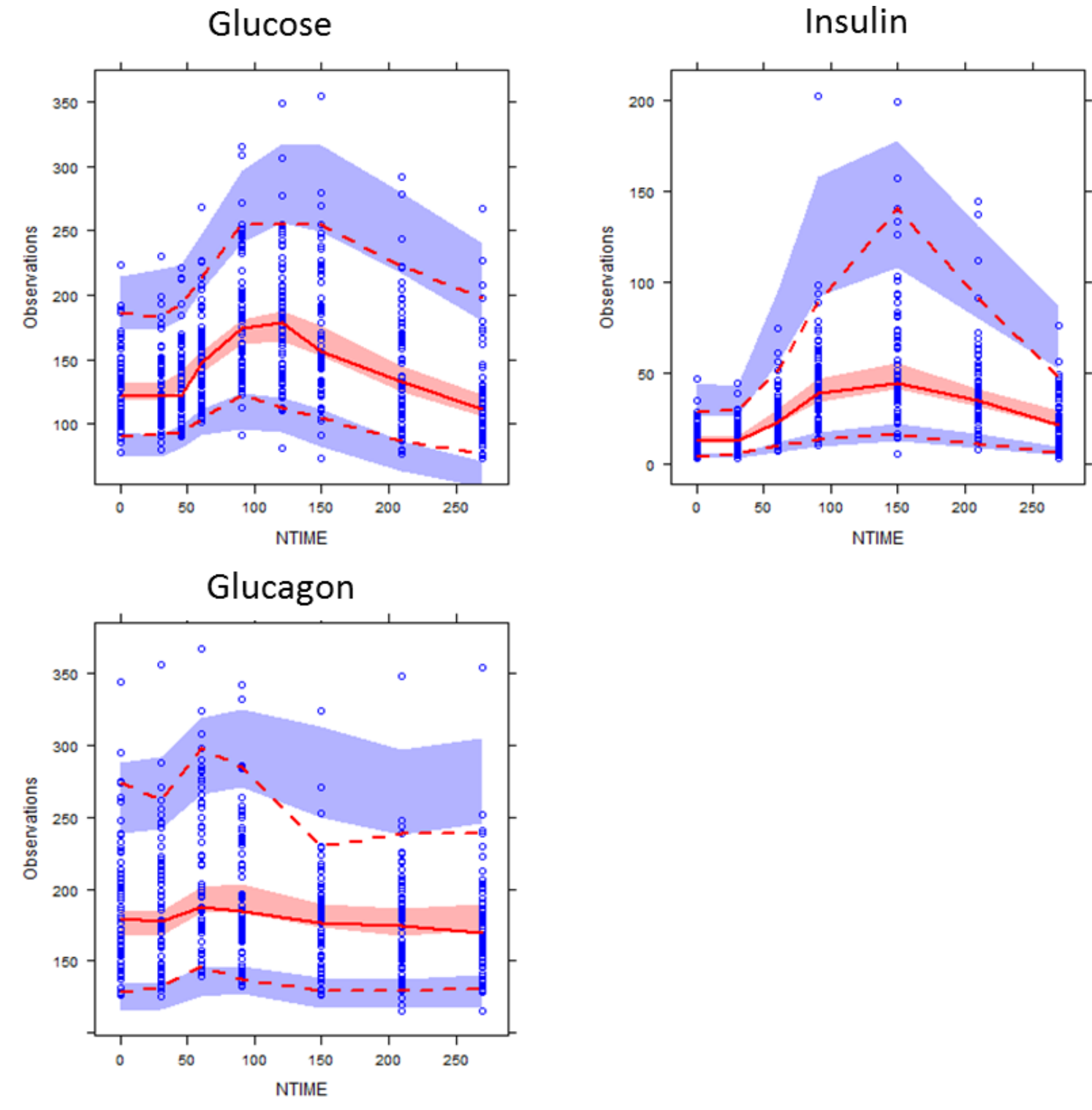


Figure 5. VPC: glucose, insulin and glucagon profiles at study week 4 following a standardised breakfast (liraglutide 1.8 mg arm).

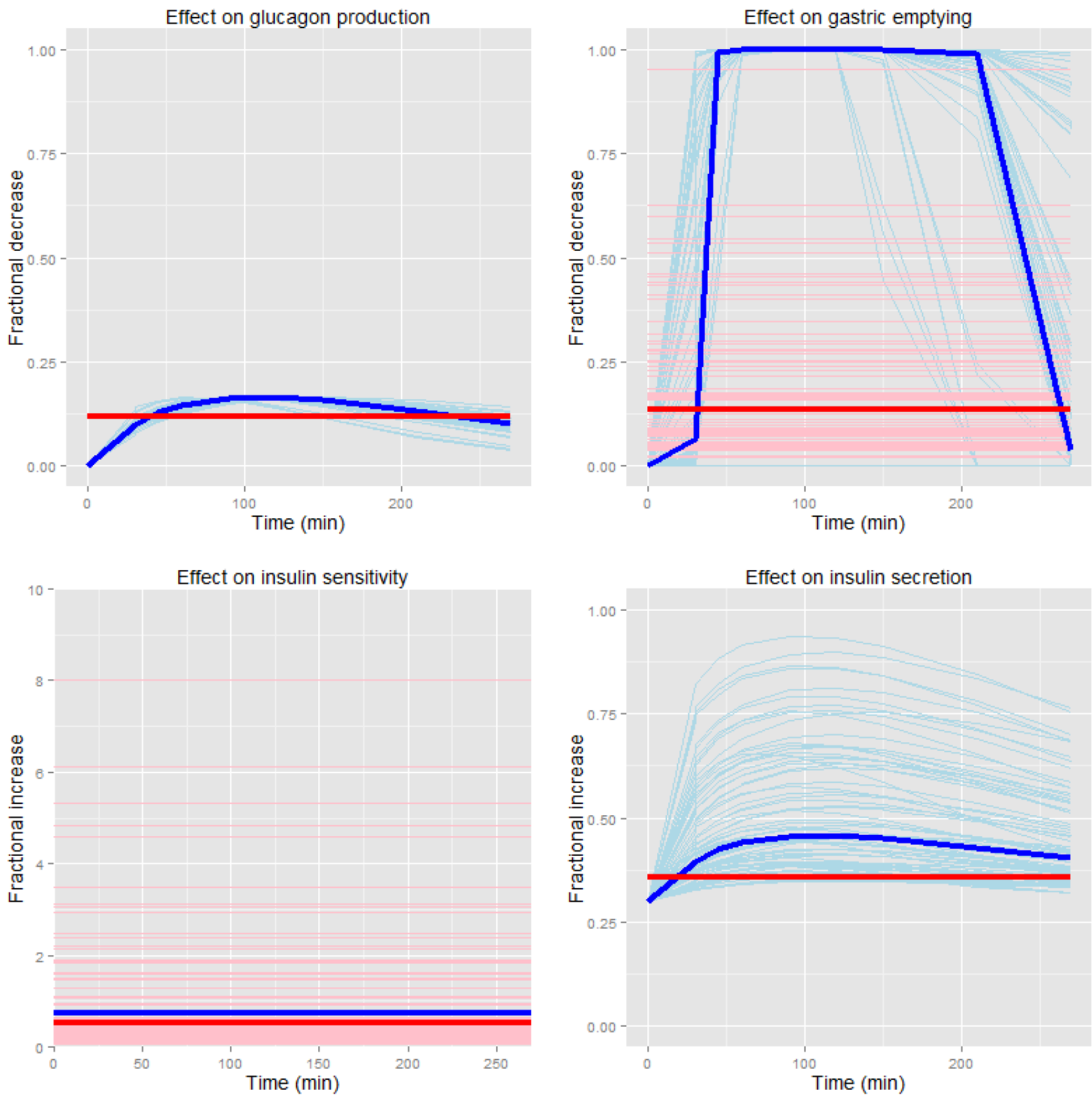


Figure 6. Comparison of estimated effects of lixisenatide (blue) and liraglutide (red) at different sites over time. Thin lines: individual profiles, thick line = median.

Simulations

were performed for comparison of lixisenatide's (Figure 7) and liraglutide's (Figure 8) differential glycaemic effects in the post-prandial situation. Each panel shows the change in glucose profiles after "deleting" one effect site versus the total effect.

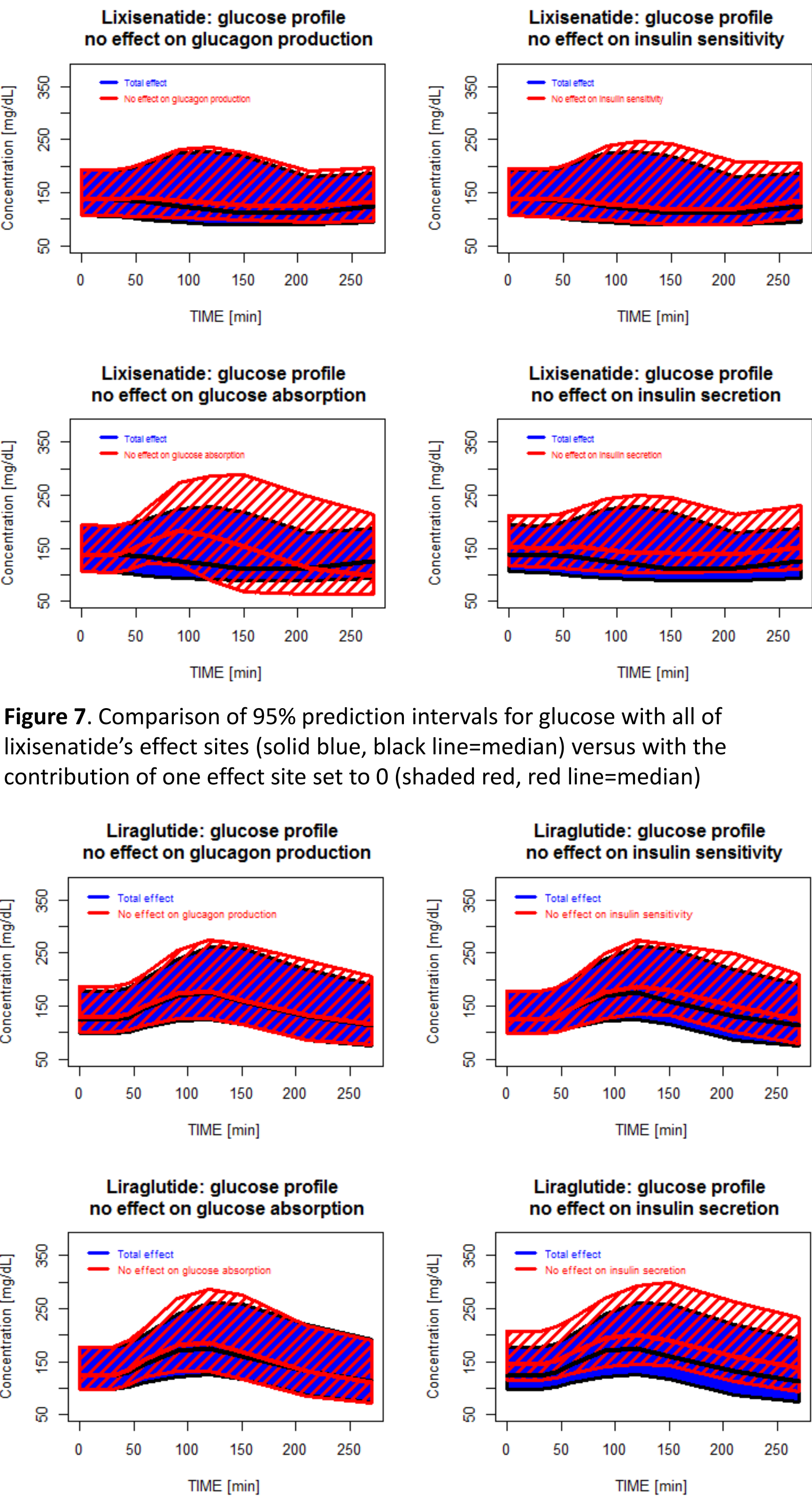


Figure 7. Comparison of 95% prediction intervals for glucose with all of lixisenatide's effect sites (solid blue, black line=median) versus with the contribution of one effect site set to 0 (shaded red, red line=median)

CONCLUSIONS

- The IGI+glucagon (IGIG) model was able to adequately describe glucose, insulin and glucagon profiles in type 2 diabetic patients.
- The same effect sites were identified for lixisenatide and liraglutide in the meal test situation.
- The relative importance of effect sites differed:
 - Liraglutide, by primarily increasing insulin secretion in both the fasting and the prandial phases (i.e., *independently of meal*), behaves like a non-prandial GLP-1 agonist.
 - Lixisenatide exhibited a profound effect on post-prandial glycaemia, mainly mediated by delaying gastric emptying, as previously reported for prandial GLP1 agonists.

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