

Integrated model of glucose homeostasis in type 2 diabetics including the effect of exogenous insulin

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Background

- Diabetes is a metabolic disorder characterised by elevated blood glucose levels. Thus the primary aim of treatment is to control the blood glucose and obtain normal or near-normal blood glucose levels, for example using exogenous insulin.
- Insulin therapy for diabetes patients is designed to mimic the endogenous insulin response of healthy subjects and thereby generate normal or near-normal blood glucose levels.
- In order to predict the blood glucose in insulin-treated type 2 diabetes mellitus (T2DM) patients, it is essential to know the effect of exogenous insulin on blood glucose.

Aim

- To develop a model to describe the 24 hour glucose profiles for T2DM patients receiving exogenous insulin therapy.

Methods

- Data from two trials were analyzed. In both trials meal tolerance tests (MTTs) were used as the experimental setup.
- Trial 1:** MTTs were performed in 16 T2DM patients. Biphasic insulin aspart was given immediately before breakfast, lunch, and dinner [2].
- Trial 2:** MTTs were performed in 13 T2DM patients. Biphasic insulin aspart was administered at breakfast and dinner [4].

- A semi-mechanistic, integrated glucose-insulin (IGI) model has previously been developed to describe MTTs for T2DM patients. The IGI model consists of glucose and endogenous insulin compartments and control mechanisms in the form of effect compartments [3]. The IGI model was extended to allow incorporation of exogenous insulin and its effects on blood glucose. A previously published pharmacokinetic model for insulin aspart [1] was applied assuming that the effect of insulin aspart and endogenous insulin were similar.

Results

- The 24 hour glucose profiles for insulin treated T2DM patients were described by extending the IGI model with two new modules :

 - A module for exogenous insulin.
 - A module to describe the hyperglycemia during the early morning known as the "dawn phenomenon". This phenomenon was described by including a modulator function to describe the circadian rhythm of endogenous glucose production seen in T2DM patients [5].

- Time courses for the plasma glucose, exogenous insulin and endogenous insulin from the two trials are shown in figure 1 together with the geometric mean of the individual predictions.

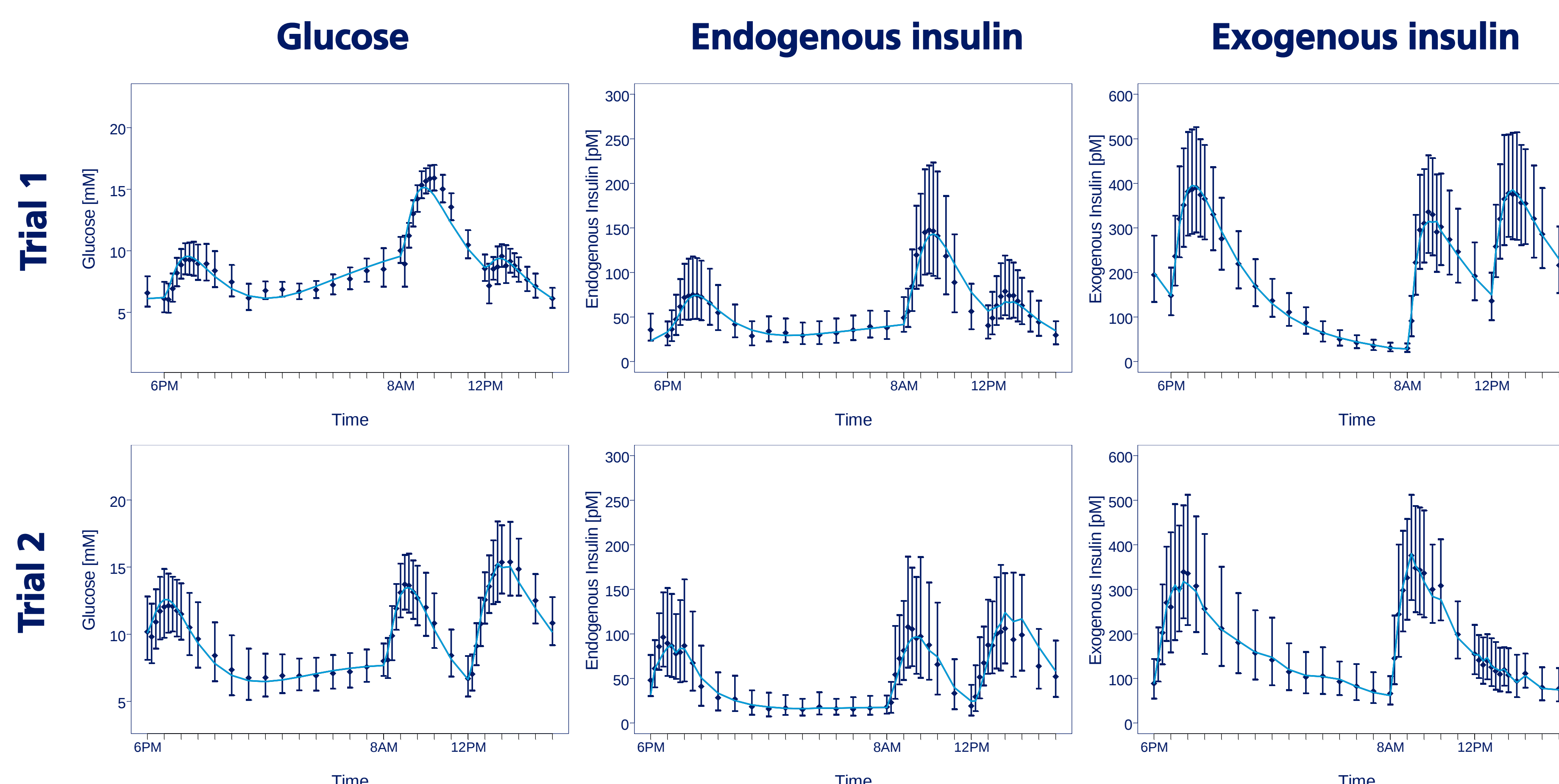


Figure 1: Time courses for plasma glucose, exogenous insulin and endogenous insulin concentrations for the two trials. The lines show the geometric mean of the individual predictions.

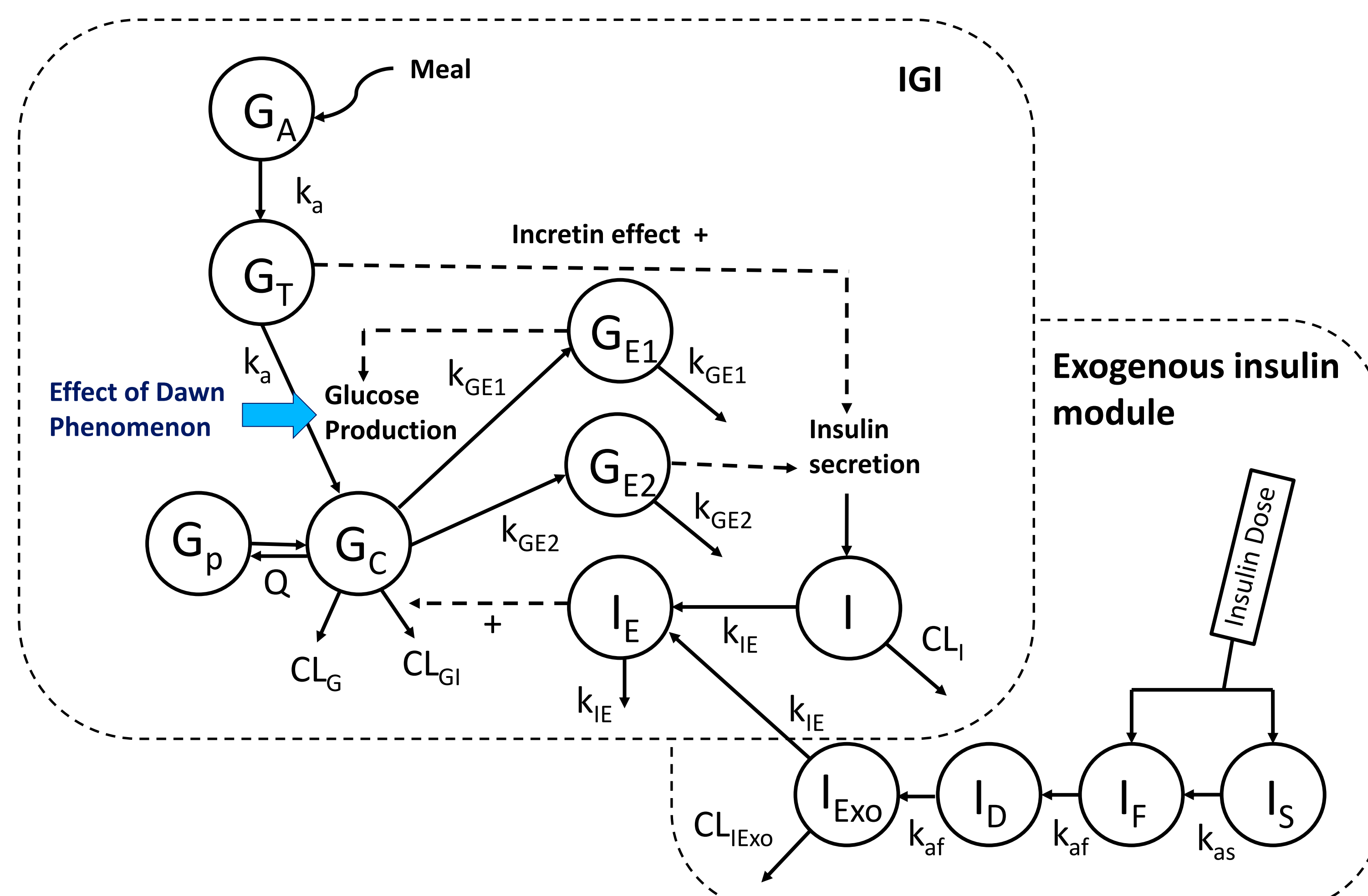


Figure 2: Schematic presentation of the integrated model with a component for exogenous insulin.

Conclusion

- A model enabling the description of 24 hour glucose profiles for T2DM patients receiving exogenous insulin was successfully developed.
- The inclusion of the effect of exogenous insulin on glucose homeostasis makes the model a useful tool for clinical trial simulation to predict the effect of different insulin treatments.

References

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