In silico modeling of patients with type 1 diabetes mellitus

Joannet Onvlee[1,2], Helga Blauw[2,3], Niels Middelhuis[4], Hans Zwart[4]
[1]Faculty of Science and Technology, University of Twente, [2]Inreda Diabetic, [3]Academic Medical Center,
[4]Faculty of Electrical Engineering, Mathematics and Computer Science, University of Twente

Introduction

Inreda Diabetic BV (Goor, The Netherlands) is developing a bi-hormonal artificial pancreas (closed-loop system) to regulate the blood glucose level in patients with type 1 diabetes mellitus. For the development and testing of this new medical device, a simulation model of the glucose-insulin-glucagon dynamics is helpful. Such a model will help to understand the medical device interactions on the glucose regulation and will provide information on the simulated responses to various stimuli. Therefore, the aim of this study was to develop a simulation model of type 1 diabetes.

Methods

Several previously published models were reviewed to identify usable models [1,2]. These models simulate the glucose regulation of patients with diabetes and have been used for in silico testing of glucose controllers of closed-loop insulin infusion systems. In addition to insulin, the glucose controller of Inreda Diabetic also uses glucagon to regulate the glucose level. Most reviewed models, however, do not simulate this part of the glucose regulation. The UVA/Padova model has been extended with the glucagon dynamics [3], but this part of the model was based on non-published assumptions and the reliability is unknown. We chose to develop our own simulation model based on the UVA/Padova model.

Results

The mathematical representations of the three main physiological subsystems – the dynamics of the glucose, insulin and glucagon processes – were obtained and implemented in Simulink (Matlab, MathWorks). The total model is divided into 10 subparts and consists of 14 differential equations. In comparison to the UVA/Padova model, changes were made in the subcutaneous uptake of insulin and glucagon and it was chosen to use the glycemic index to simulate the intake of carbohydrates. The liver was modeled in accordance with the UVA/Padova model. Furthermore, the parameters for the subcutaneous glucagon infusion and glucagon kinetics in the blood plasma were estimated with clinical data [4]. An ARMAX model was used to estimate these parameters with the least squares method. Although a relatively wide variation in the parameter values was found, the results were realistic and can be used in the model. On the other hand, not all equations could be explained physiologically and the simulation results showed that the glucose influence on the liver was too strong, and so our current work focusses on these issues.

Conclusion

A simulation model was developed that represents the glucose regulation in patients with type 1 diabetes mellitus. Current work concentrates on the implementation of the liver and the parameter estimation of the other model subparts. This model has the potential to provide a substantial basis for the in silico testing and further development of the bi-hormonal artificial pancreas.

References

[1] M.E. Wilinska, and R. Hovorka, "Simulation models for in silico testing of closed-loop glucose controllers in type 1 diabetes." in *Drug Discovery Today: Disease Models*, vol. 5, no. 4, 2008, pp. 289–298.
[2] P. Colmegna, and R. S. Sánchez Peña, "Analysis of three T1DM simulation models for evaluating robust closed-loop controllers." *Computer Methods and Programs in Biomedicine*, vol. 113, no. 1, 2014 pp. 371–382.
[3] C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, and C. Cobelli. "The UVA/PADOVA type 1 diabetes simulator: new features." *Journal of Diabetes Science and Technology*, vol. 8, no. 1, 2014, pp. 26–34.
[4] H. Blauw, I. Wendl, J.H. Devries, T. Heise, and T. Jax (2016). "Pharmacokinetics and pharmacodynamics of various glucagon dosages at different blood glucose levels." *Diabetes, Obesity and Metabolism*, vol. 18, no. 1, 2016, pp. 34–39.