Modelling of postprandial glucose and insulin dynamics

SUMMARY

A complex regulatory system is in play to maintain and control blood glucose levels under different physiological conditions. Currently existing whole-body mechanistic models of the glucose regulatory system generate quantitative information on glucose-insulin dynamics whilst capturing the mechanistic link between glucose and insulin. However, these models do not include the effect of amino acids (AAs), which have been recognized as important dietary components influencing glucose regulation in various health phenotypes. Incorporating the postprandial effect of AAs and protein is essential given their impact on both acute and long-term postprandial glucose metabolism. In addition, these mechanistic models have mainly been used to describe population averages, thus disregarding the heterogeneity in individual responses. In this thesis, we used a computational modelling approach to allow personalized simulation of postprandial glucose, insulin, and AA responses following challenge tests containing AAs or protein in various health phenotypes using a whole-body mechanistic model of glucose homeostasis. Furthermore, we explored whether the addition of a data-driven model could improve the predictive performance of the mechanistic models.

In **Chapter 2**, we performed a systematic literature search to identify intervention studies reporting glucose and insulin concentrations following acute ingestion and/or intravenous infusion of AAs in healthy adults and those living with obesity and/or type 2 diabetes (T2DM). We identified and extracted glucose and insulin time-series data from 55 studies that examined the effects of leucine (n=6), isoleucine (n=1), alanine (n=6), glutamine (n=1), arginine (n=28), lysine (n=1), glycine (n=2), proline (n=1), phenylalanine (n=1), glutamate (n=3), branched-chain AAs (n=4), and multiple individual AAs (n=1) on glucose and insulin concentrations. The data showed that oral ingestion of most individual AAs induced an insulin response but did not alter glucose concentrations in healthy participants. Specific AAs, such as leucine and isoleucine, when co-ingested with glucose exerted a synergistic effect on the postprandial insulin response, and attenuated the glucose response more compared to glucose intake alone in healthy participants. Furthermore, oral AA ingestion as well as intravenous AA infusion was able to stimulate an insulin response and decrease glucose concentrations in T2DM and obese individuals. The extracted glucose and insulin time-series data was made publicly available.

The postprandial glucose and insulin responses to identical meals can vary significantly across individuals. Certain dynamic features of these responses have been shown to be indicative of the state of the glucose regulatory system and therefore relevant for targeted lifestyle intervention. Currently, this heterogeneity is overlooked due to a lack of methods to quantify the interconnected dynamics in the glucose and insulin time-courses. In **Chapter 3**, we personalized a physiology-based mechanistic model of the glucose regulatory system to elucidate the heterogeneity in individuals' postprandial responses to an oral glucose tolerance test (OGTT) using a large population of people who have overweight or obesity (n = 738) from the DIOGenes study. To transition from population averages towards describing individual response patterns, we developed a systematic parameter selection pipeline that may also be generalized to other biological systems. We showed that personalized models were able to capture the postprandial glucose and insulin responses more accurately compared to the population-level models. Furthermore, the estimated model parameters captured relevant features of individuals' metabolic health such as gastric emptying, endogenous insulin secretion, and insulin-dependent glucose disposal into tissues. The latter two also showed a significant association with the Insulinogenic index and the Matsuda insulin sensitivity index, respectively.

While physiology-based mechanistic models perform well in response to oral glucose challenges, interactions with other nutrients, like AAs and protein have not been considered yet. In **Chapter 4**, we developed a mechanistic model of the glucose homeostasis that incorporates and captures the postprandial effects of AAs and protein intake. New terms, accounting for the effect of AAs on insulin secretion and liver glucose production were introduced and the model was applied to postprandial glucose and insulin time-series data following different AA challenges (with and without co-ingestion of glucose), dried milk protein ingredients, and dairy products. We showed that this novel model was able to accurately describe the postprandial glucose and insulin dynamics, whilst providing insight into the physiological processes underlying meal responses.

While both "bottom-up" mechanistic and "top-down" data-driven techniques offer distinct benefits in untangling the complex interactions underlying disturbances in glucose homeostasis, a combined approach has yet to be explored. In **Chapter 5**, we used a sequential combination of a mechanistic and a data-driven modelling approach to quantify individuals' glucose and insulin responses to an OGTT, using cross-sectional data from a large observational population-based cohort, the Maastricht Study. We showed that the addition of

a data-driven machine learning model did not improve predictive performance. The personalized mechanistic models consistently outperformed the data-driven and the combined model approaches, demonstrating the strength and suitability of "bottom-up" mechanistic models in describing the dynamic glucose and insulin responses to OGTTs.

Tissue-specific insulin resistance phenotypes (predominantly muscle or liver) have been shown to interact with diet to determine changes in metabolic outcome and have shown distinct glycemic responses to challenge tests. In **Chapter 6**, we applied our novel model (developed in Chapter 4), to simulate and understand mechanistic differences between muscle insulin resistance and liver insulin resistance, using postprandial glucose, insulin, and AA time-series data following a high-fat-mixed meal in individuals from the PERSON study. We showed that our model accurately simulated glucose and insulin response following ingestion of a high-fat mixed meal, and predicted a difference in physiological processes such as gastric emptying and insulin-dependent glucose uptake into tissues, and insulin secretion between tissue-specific insulin-resistant metabolic phenotypes. Insight into the biological mechanisms underlying tissue-specific insulin resistance phenotypes is important due to the differential response to lifestyle and pharmacological interventions aimed to increase cardiometabolic health and/or insulin sensitivity. Personalized models could therefore play a key role in the transition towards precision nutrition, not only by assessing the effects of an intervention, but also providing dietary advice aimed to prevent (further) deteriorations in the glucose regulatory system.