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Model-based analysis of postprandial glycemic response dynamics for different types of food

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SUMMARY

Background & aims: Knowledge of postprandial glycemic response (PPGR) dynamics is important in nutrition management and diabetes research, care and (self)management. In daily life, food intake is the most important factor influencing the occurrence of hyperglycemia. However, the large variability in PPGR dynamics to different types of food is inadequately predicted by existing glycemic measures. The objective of this study was therefore to quantitatively describe PPGR dynamics using a systems approach. *Methods:* Postprandial glucose and insulin data were collected from literature for many different food products and mixed meals. The predictive value of existing measures, such as the Glycemic Index, was evaluated. A physiology-based dynamic model was used to reconstruct the full postprandial response profiles of both glucose and insulin simultaneously.

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Results: We collected a large range of postprandial glucose and insulin dynamics for 53 common food products and mixed meals. Currently available glycemic measures were found to be inadequate to describe the heterogeneity in postprandial dynamics. By estimating model parameters from glucose and insulin data, the physiology-based dynamic model accurately describes the measured data whilst adhering to physiological constraints.
Conclusions: The physiology-based dynamic model provides a systematic framework to analyze postprandial glucose and insulin profiles. By changing parameter values the model can be adjusted to simulate impaired glucose tolerance and insulin resistance.

1. Introduction

The metabolic and hormonal response after a meal are important in nutrition management and diabetes research, care and (self) management [1] and for sports performance [2]. Generally, dietary guidelines advice to consume foods that elicit moderate and prolonged postprandial glycemic responses (PPGR) such that the occurrence of wide glucose excursions is minimized. This is especially important for diabetes patients who need to ensure tight glycemic control to limit diabetic complications [3,4]. In order to prevent hyperglycemia, information about the height and timing of the postprandial glucose peak is important for diabetes patients that are dependent on exogenous insulin administration to suppress postprandial glycemia [1]. This information is also important for the large population of people that are in a pre-diabetic state, since these patients may benefit from lower glycemic response profiles in order to refrain from developing diabetes [5]. On the other hand, the duration of the postprandial glucose peak is of importance during exercise: a sustained and steady release of glucose is beneficial for performance in endurance sports [2].

To keep control of the postprandial response, knowledge of the metabolic effect that different foods have is required. A predictor that is frequently used in daily life to predict postprandial glycemia is the carbohydrate content. However, large differences in the extent to which different carbohydrate sources raise the blood glucose level have been observed: many studies have shown that consumption of equi-carbohydrate portions of food elicit clearly different glycemic responses [6–8]. Therefore, several nutritional rating systems such as the Glycemic Index (GI) [9,10], the Glycemic Load (GL) [11,12] and the Glycemic Glucose Equivalents [13] have been proposed. These measures are derivations of the 2 h postprandial area under the glucose curve (AUC). Systematic studies [14,15] have shown that both GI and GL are stronger predictors of postprandial glucose and insulin levels than carbohydrate content alone and that the GL outperforms the GI for both single foods and composite meals.

However, a large variability in the postprandial response within and among individuals is observed, as was recently reported by Zeevi et al. [16]. This underlines the importance of developing an alternative method to understand postprandial dynamics that considers heterogeneity in both composition and amount of food as well as the metabolic status of the subject. The degree of insulin sensitivity is a major controlling factor in PPGR dynamics. Therefore, glucose and insulin should be assessed simultaneously, as is also done in e.g. clamping methods [17] and for the estimation of insulin sensitivity indices such as HOMA-IR (homeostatic model assessment of insulin resistance) [18] and MISI (Matsuda Insulin Sensitivity Index) [19].

Hereto, we propose the use of a physiology-based dynamic modeling (PBDM) approach to improve the understanding of PPGR dynamics assessed from sampled postprandial glucose and insulin data. Our PBDM approach combines physiological knowledge of the digestive system, absorption and the

glucose-insulin regulatory system, with carbohydrate content and observed glucose and insulin response profiles for a wide variety of common food products and mixed meals.

2. Materials and methods

2.1. Data collection

Postprandial time course data of various single (one separate type of food) food products and mixed meals in healthy subjects were collected from literature. Datasets were included when they contained both postprandial plasma glucose and insulin concentration measurements. We performed an extensive literature search (using the terms 'glucose', 'insulin', 'postprandial response', 'food' and 'meal') to find studies that measured postprandial time course data in response to a carbohydrate (containing) meal. Only publications in which the subjects were classified as healthy were included, according to the following criteria: 1) normal glucose tolerance (fasting plasma glucose level < 5.6 mmol/L, postprandial plasma glucose peak < 11.0 mmol/L and 2 h postprandial plasma glucose level < 7.8 mmol/L [20–22]; 2) normal insulin sensitivity (fasting plasma insulin level < 15 mU/L, postprandial plasma insulin peak < 100 mU/L and 2 h postprandial plasma insulin level < 50 mU/L [23,24]); 3) normotensive (systemic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg [25]); 4) normal hemoglobin level (HbA_{1c} < 6.5% [26]); 5) non-obese (BMI < 30.0 kg/m^2 [27]); 6) no family history of diabetes; 7) free of apparent diseases; 8) free of regular medication; 9) stable body weight and no change in dietary habits in the three months preceding the measurements; and 10) non-pregnant state of female subjects. These criteria are conform current guidelines, adhering to the same standards and requirements as studies involving Oral Glucose Tolerance Test (OGTT) protocols.

2.2. Physiology-based dynamic model describing postprandial glucose and insulin dynamics

To analyze the collected postprandial glucose and insulin data simultaneously, we propose to use a computational modeling approach and hypothesize that it is more robust in describing postprandial dynamics than currently used AUC-based methods. We aimed for a relatively simple model for which predictions adhere to physiological constraints and that is applicable during everyday life conditions.

We adapted our previously developed model by Maas et al. [28] describing the glucose-insulin kinetics as a function of time in response to healthy subjects OGTTs. However, though the response curves for a standardized OGTT have relative simple kinetics, the postprandial dynamics after consumption of real food products and mixed meals are more complex. Hereto, the gastric emptying equation (see Eqs. (4) and (5)) in Supplemental Note 1) was adjusted such that more dynamic gastric emptying profiles could be simulated. This model is schematically illustrated in Fig. 1. Phenomenologically, the gastric emptying equation lumps together many biological processes in the gastrointestinal tract, which could include incretins, but also bile acids. The gastric emptying was divided into two terms (as is described in detail in Supplemental Note 1): the first term represents fast release of digested carbohydrates into the gut (e.g. in response to simple carbohydrates), while the latter represents a more steady release of carbohydrates (e.g. in response to consumption of complex carbohydrates or due to starch encapsulation by lipids or proteins) [29].

2.3. Model calibration through parameter estimation

In order to model the postprandial response after food intake, the model parameters had to be adjusted to the different types of food. Since the initial PBDM was developed to describe OGTT response data for healthy persons [28] and the collected data in this study have also been measured in normal glucose tolerant subjects, we assumed that insulin sensitivity and beta-cell function were not affected by food consumption. Therefore, the model parameters representing these processes remained unchanged (parameter values are listed in the Supplemental Table in Supplemental Note 1). Only the model parameters related to food digestion and subsequent glucose absorption are allowed to change during the recalibration of the model. These parameters represent rate constants of glucose release in the gut from both fast absorbed carbohydrates (k_1) and more slowly absorbed carbohydrates (k_{13}), the rate constant of

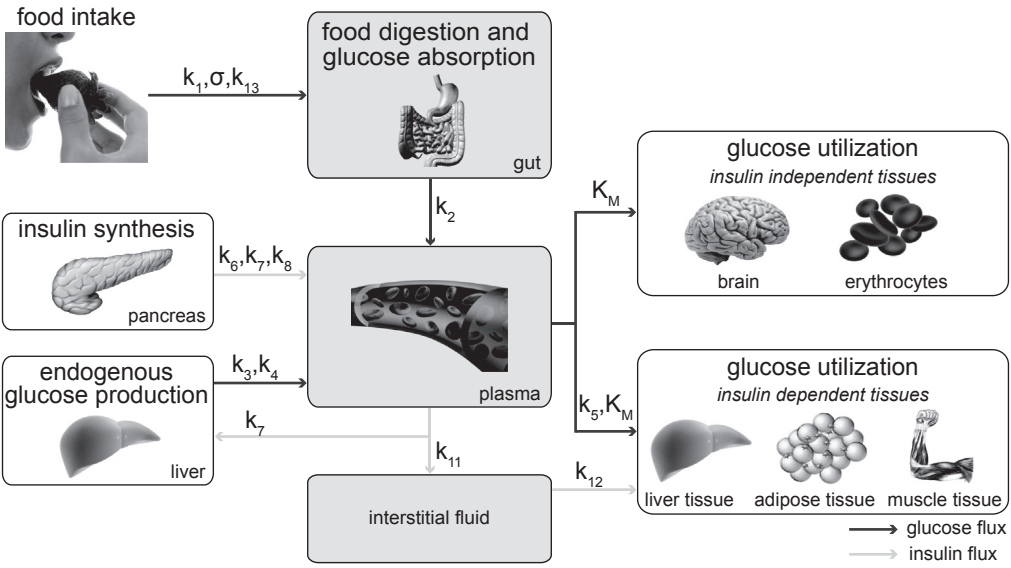

Fig. 1. Schematic visualization of the mathematical model describing postprandial glucose metabolism. The mathematical model comprises three compartments (shaded background) depicted in the central column that represent the compartments in which the glucose and insulin balances are computed. The corresponding glucose and insulin fluxes (exchange between compartments) are visualized in dark gray and light gray, respectively, and are labeled with the model parameters that govern these fluxes adapted with permission from [28].

gastric emptying (k_2) and the shape factor of the gastric emptying pattern (σ) (see Supplemental Note 1). These four parameters were re-estimated by Maximum Likelihood Estimation, during which the weighted squared difference (between the modeled glucose and insulin profiles and the respective glucose/insulin data) was minimized. The model is considered acceptable if 95% of the glucose data points lie within an acceptance range of ±20% of the corresponding model value. This accuracy window is consistent with the accuracy of blood glucose meters [30]. In addition, this range also encompasses the observed inter-individual variance [16]. For insulin we chose a wider acceptance range of ±25%, which is consistent with the larger variability in insulin measurements observed in literature [31].

The PBDM and the optimization procedure were implemented in MATLAB (R2013b, The MathWorks, Natick, Massachusetts) and utilized the *lsqnonlin* method from the Optimization Toolbox. For more details on the full methodology, the reader is referred to Maas et al. [28].

2.4. Kinetic properties to quantify postprandial dynamics

The PBDM yielded continuous profiles for the postprandial phase for both glucose and insulin. To quantitatively describe these dynamics, we propose the use of the following kinetic properties to supplement the classically used AUC:

1) peak height: maximum concentration during the postprandial period;
2) peak duration: time interval during which the concentration is higher than 20% of the peak height (with respect to the baseline fasting level). This property indicates how long the hyperglycemia/hyperinsulinemia lasts while taking fluctuations from baseline level into account;
3) rise time: time interval from the start of the postprandial period (start of the food consumption) to the occurrence of the peak height.

These kinetic properties are illustrated in Fig. 3g. Sharp and well-defined peaks have a shorter peak width, shorter rise time and usually a larger peak height than less profound peaks.

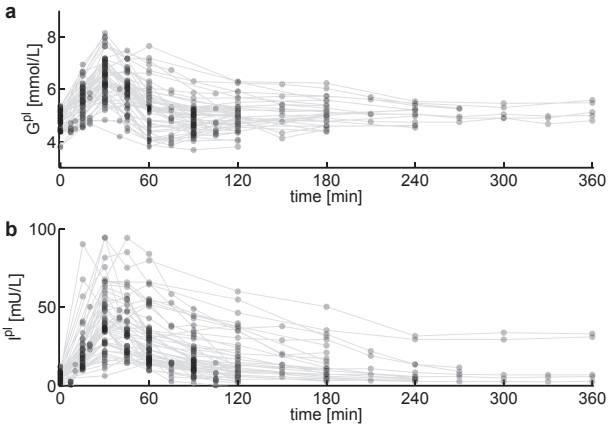

Fig. 2. Distribution of postprandial response data for all 53 included food products and meals. In this density plot, data for glucose (**a**) and insulin (**b**) are visualized over time for each included food product and meal [6–8,32–46], originating from in total 240 subjects. The data points (dots) are color-coded such that a richer shade corresponds to more datasets overlapping in this time–concentration region. The solid lines indicate the time course of the postprandial response profile for each food product and meal separately.

3. Results

3.1. Wide range in postprandial response dynamics after food consumption

We collected 53 postprandial response datasets from 18 publications [6–8,32–46] in which both glucose and insulin were measured after consumption of either a single food product or a mixed meal. Figure 2 shows the heterogeneity in postprandial dynamics in both the glucose and insulin response. Supplemental Table 1 provides a detailed overview of the included datasets. A digital version of all included data (glucose and insulin mean ± standard deviation for all time points) is available in Supplemental Database 1. Additional datasets comprising of only glucose measurements and OGTTs have been included in this database as well.

Note that the available postprandial datasets differ strongly in time resolution (the time interval between consecutive measurements ranges from 7 to 60 min) and measurement duration (ranging from 2 to 6 h after food consumption).

3.2. Evaluating existing glycemic measures to describe postprandial glycemia

We first evaluated currently available glycemic measures in their efficacy in describing postprandial glycemia using the collected datasets. Figure 3a describes the postprandial glucose profiles for food consumptions that all contain 50 g available carbohydrates. The kinetics of the postprandial glucose profiles deviate largely among different foods. Although commonly used, the carbohydrate content is not a unique determinant of postprandial response dynamics.

Figure 3b demonstrates that postprandial profiles resulting from different meals may have a comparable 2 h-iAUC, yet distinctly different dynamics. Also AUC-derived measures, such as the Glycemic Index (Fig. 3c), do not distinguish properly between different postprandial response profiles. Despite being classified with the same GI and carbohydrate dose, the peak height and rise times of the profiles in Fig. 3c vary, and especially the peak width differs largely between these foods.

Moreover, assessment of the AUC highly depends on the sampling interval during the postprandial time window. Since postprandial data are often measured sparsely with large time intervals, the precise height and timing of the peak are often unknown. Figure 3d demonstrates the effect of a sampling interval that was artificially reduced to 30 min (gray) rather than the original 15 min (black), and shortening the measurement duration to 120 min. Reduced temporal resolution results in a biased view of the postprandial dynamics: the postprandial glucose peak is reached at 45 min in the original

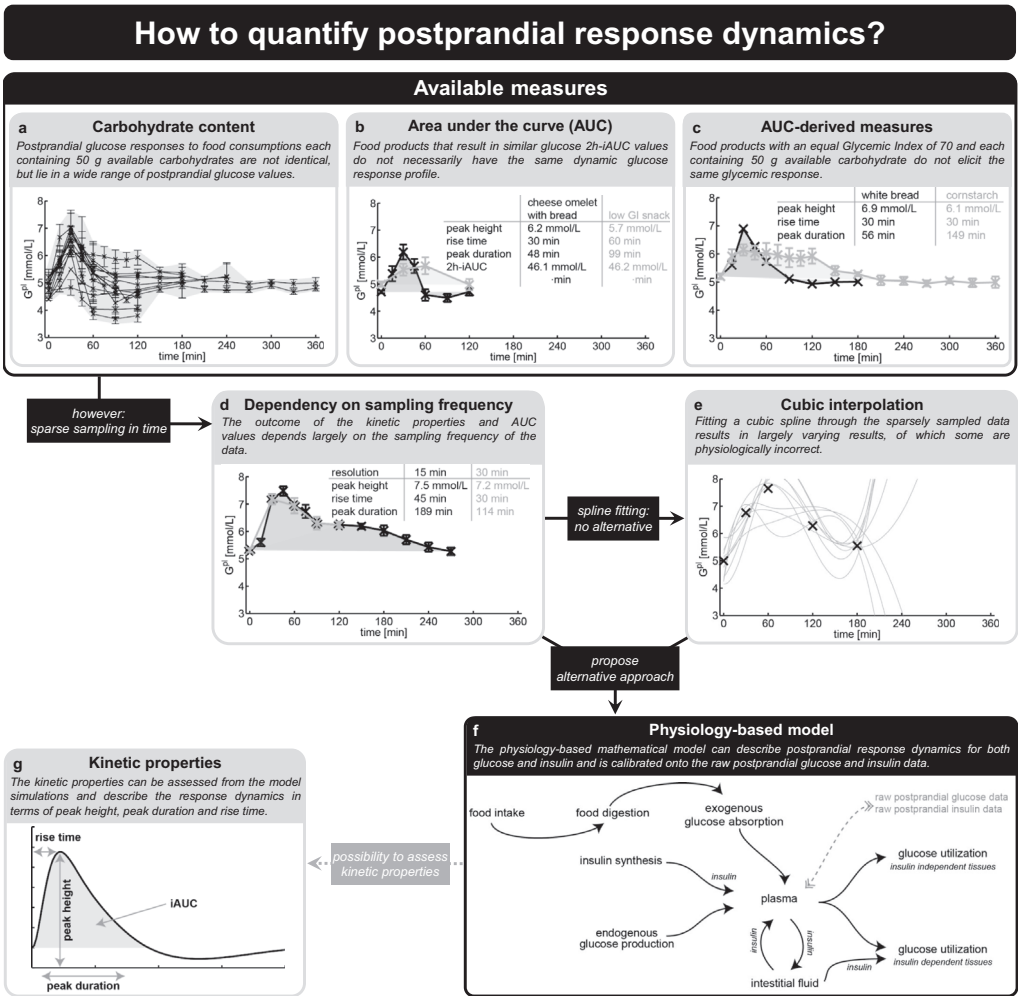

Fig. 3. How to quantify postprandial response dynamics? Panel **a**–**c** present currently available measures of postprandial response dynamics. In panel **a** datasets (black; error bars represent mean ± standard deviation per food and per time point) comprising of 50 g carbohydrate containing food are depicted, ranging from plain bread, fruit juice and rice up to complete breakfasts [7,8,33,35,39,43]. The gray area depicts the large range in which these postprandial responses lie. Panel **b** depicts datasets with similar 2 h-iAUC values assessed from the average glucose data for a cheese omelet with bread meal (black) [44] and a low GI snack (gray) [40]. The 2 h-iAUC is approximated using trapezoidal numerical integration (conform current standards [62], only the incremental area – above fasting level – is included). Panel **c** presents the assessed kinetic properties for two different types of food both having a Glycemic Index of 70 and containing 50 g of digestible carbohydrate: white bread [7] is shown in black, cornstarch [43] in gray. Panel **d** depicts the dependency on sampling frequency. The kinetic properties are assessed for the postprandial glucose profile for a high GI breakfast containing 65 g digestible carbohydrates. The original dataset [38] is shown in black, and in gray a subset of the same dataset is shown that has a reduced temporal resolution and shorter measurement duration. in panel **e**, spline fitting (gray) is examined in the case of a wheat lunch [36] (data shown in black). Panel **f** illustrates the physiology-based dynamic modeling approach in terms of how the underlying fluxes regulate glucose and insulin in the plasma during the postprandial state. Panel **g** illustrates the kinetic properties to quantify the characteristic dynamics of postprandial profiles.

data, whereas the down-sampled dataset indicates it already at 30 min. Moreover, assessment of the overall kinetics (as reflected by rise time and peak duration, Fig. 3g) is biased as well. Spline fitting onto the measured data may provide a possible solution to deal with sparse data and to account for missing values. Figure 3e demonstrates the fitting of several cubic smoothing splines through the

experimentally observed glucose data points. However, using artificial interpolation techniques to fit arbitrary splines through data points does not yield physiologically correct profiles.

The currently available methods are theoretically inaccurate to quantify the difference between varying postprandial glucose response profiles. Furthermore, these only depend on the glucose response data and do not make use of physiological information contained in the insulin response. Therefore, we utilize a physiology-based dynamic model (Fig. 3f) to assess postprandial glucose and insulin dynamics simultaneously, whilst adhering to prior knowledge on the digestive system, absorption and the glucose-insulin regulatory system.

3.3. The physiology-based dynamic model (PBDM) describes the heterogeneity in postprandial dynamics well

The PBDM has been fitted to each of the 53 collected postprandial response datasets that each represent one specific food product or mixed meal. The simulated postprandial glucose and insulin profiles are documented in Additional file 4: Fig. S1 in combination with the data that it was fitted to. The model simulations agree well with the data for a wide variety of food products and mixed meals. The resemblance (defined as the relative difference $R = 1 - \frac{\sum_x^{N_x}\sum_t^{N_t}\frac{|y_x(t)-\mu_x(t)|}{\mu_x(t)}}{N_x N_t}$) between the model and the measured data is $89 \pm 6\%$ (range 71–98%) for the combined postprandial glucose and insulin data points. In general, glucose is fitted better ($94 \pm 4\%$; range 79–99%) than insulin ($83 \pm 9\%$; range 54–96%). The values of the optimized model parameters corresponding to each meal are listed in Supplemental Database 2.

The model performs well for a wide variety of common food products and mixed meals. In Fig. 4 two different scenarios of model simulations are highlighted. Figure 4a–4b demonstrates that consumption of the same amount of carbohydrates can result in drastically different postprandial dynamics. As a

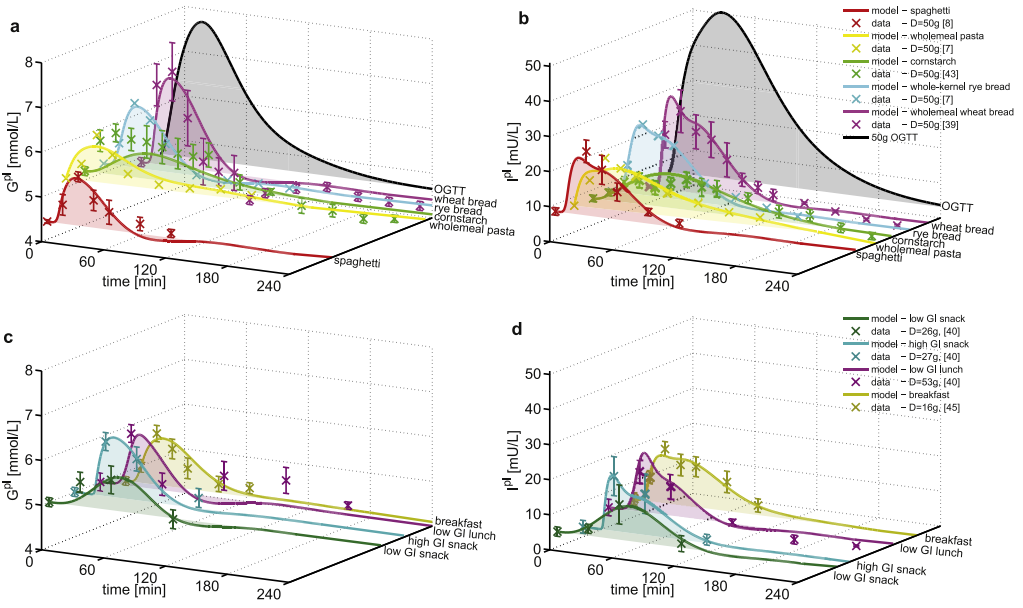

Fig. 4. The physiology-based dynamic model describes the heterogeneity in postprandial dynamics well. Panels **a**–**b** show the postprandial response for various equi-carbohydrate foods and panels **c**–**d** for foods with varying carbohydrate content. Simulated (solid lines) and observed (error bars: mean ± standard deviation) postprandial glucose (**a**,**c**) and insulin (**b**,**d**) response profiles for a selection of food products and meals. The OGTT model simulation (**a**–**b**) is included in black to serve as reference. Panels **a-b** comprise situations in which 50 g available carbohydrates are present in the ingested food [7,8,39,43], but result in different postprandial dynamics. Panels **c**–**d** depict the opposite situation in which the postprandial dynamics falls in a similar range, although the available carbohydrate content varies [40,45].

reference, an OGTT (based on the original model parameters of the PBDM [28]) with the same carbohydrate dose is simulated in black. Although many diabetes patients still assume that equi-carbohydrate meals elicit similar postprandial responses, and use the carbohydrate content to predict the amount of insulin that they should administer prior to a meal, both the collected literature data (see Fig. 3a) and our PBDM do not support this. We have shown that the variability in postprandial dynamics cannot be explained solely by carbohydrate dose.

On the other hand, Fig. 4c–d illustrates that similar postprandial dynamics can be elicited by meals with widely varying carbohydrate content. Especially the postprandial glucose peak heights of the four different meals match closely and lie in the range of 6.1 ± 0.2 mmol/L.

The PBDM demonstrates that it can describe many different measured postprandial profiles and proves to be flexible to describe a wide variety of kinetics as found in the literature. This is also reflected in the kinetic properties (see Supplemental Fig. 1) that were assessed from the PBDM simulations: the model accommodates for a wide range of especially the peak width and rise time parameters. The PBDM produces physiologically correct profiles for a wide variety of meals, whilst taking into account the uncertainty from sparsely sampled data.

3.4. The PBDM improves insight in the underlying metabolic fluxes

Since the PBDM has shown to agree well with both the experimental data and the biological background on the digestive and metabolic system, we explored if the model can be used to provide quantitative information about the underlying processes that have not been measured experimentally. Figure 5 shows predicted flux profiles in the intestine, pancreas and insulin-dependent tissues (of which the corresponding glucose and insulin profiles have been depicted in Fig. 4a–b). Although the amount of consumed carbohydrates is the same, the predicted glucose rate of appearance (Fig. 5a) reveals that different foods are digested at different rates. Furthermore, the dynamics in insulin synthesis (Fig. 5b) and glucose utilization rate (Fig. 5c) are closely related with the dynamics in the rate of glucose appearance. Foods that induced rapid glucose release also induced a high and rapid insulin synthesis rate (Fig. 5b). And as a consequence, the released glucose is utilized rapidly by insulin-dependent tissues (Fig. 5c). Furthermore, some fluxes show a biphasic profile, which is a propagation of the biphasic response observed in the insulin secretion flux. This biphasic profile originates from the superposition of the three separate processes underlying insulin secretion, which can be interpreted as a rapid first response from pre-formed insulin and slower secondary response from newly synthesized insulin [47].

3.5. The PBDM accounts for reduced insulin sensitivity and hyperinsulinemia

We have shown the performance of the PBDM under normal glucose tolerant, insulin sensitive conditions (i.e. for healthy subjects). The PBDM shows accurate fits of the postprandial glucose and

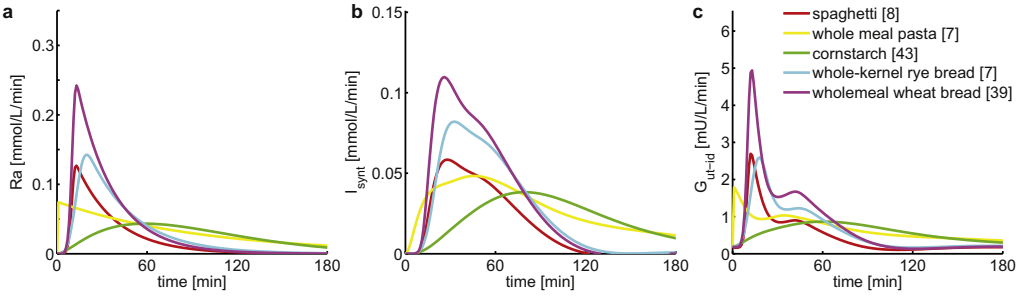

Fig. 5. The physiology-based dynamic model predicts the underlying metabolic fluxes. The predicted fluxes are displayed for foods that all contain 50 g of available carbohydrates [7,8,39,43]: rate of appearance of exogenous glucose (**a**), insulin synthesis rate (**b**) and glucose utilization by insulin-dependent tissues (**c**). These modeled fluxes correspond to the simulated glucose and insulin profiles depicted in Fig. 4a–b.

insulin response data. In general, glucose dynamics are fitted closely to the literature data, whereas there are a number of cases for which the model-to-data-fit did not satisfy our standards, especially for the insulin responses. Upon closer inspection, these datasets typically contain high glucose and high insulin responses, which the PBDM was unable to fit both at the same time. The PBDM assumed normal insulin sensitivity, whereas high glucose and high insulin responses are an indicator for reduced insulin sensitivity, for which the pancreas compensates by increasing its insulin production and secretion (hyperinsulinemia). Since the subjects included in those studies reporting high glucose and high insulin responses were classified as overweight (but not obese), it is quite possible that these subjects suffer from some degree of insulin resistance (early stage type 2 diabetes/prediabetes). This shows the need for an adjustable model in which parameters are modified to account for the metabolic status of an individual. Depending on the metabolic status, the model parameters specifying beta-cell function (which is impaired in type 1 and type 2 diabetes) and insulin sensitivity (which is reduced in pre-diabetes and type 2 diabetes) should be adjusted correspondingly. To test this hypothesis, we repeated the parameter estimation procedure, but for the current case we estimated not only the digestion and absorption related parameters, but also the model parameters governing the pancreatic beta-cell function (parameters k_6, k_7 and k_8) and insulin sensitivity (constant β).

Figure 6 demonstrates that the adjusted model can now better accommodate the simultaneously high glucose and high insulin levels as reported in the study by Nazare et al. [38] in whom non-diabetic overweight subjects were included. Hereto, the model parameters regarding insulin production were increased and simultaneously the constant representing insulin sensitivity is (slightly) reduced. This yielded an accurate fit of the first hour after food consumption, but these changes were not yet sufficient to describe the remainder of the postprandial insulin response. However, this does demonstrate that the PBDM is not only able to represent postprandial response profiles for normal glucose tolerant cases, but also for pre-diabetic cases by personalizing the system.

4. Discussion

We studied postprandial response dynamics using a model-based approach to quantify the effect of different types of food on the postprandial dynamics. Hereto we first collected data on the postprandial glucose and insulin response to a wide variety of food products and mixed meals, giving a good representation of the heterogeneity in response dynamics observed in everyday life. We employed a physiology-based dynamic model to accurately describe the postprandial dynamics whilst taking into account uncertainty due to sparse and heterogeneous data.

4.1. Postprandial variability originates from both the consumed food and person-specific conditions

The collected data revealed a large range in which the postprandial response to different food products and mixed meals falls (Fig. 2). Not only did we find a large variability among different meals,

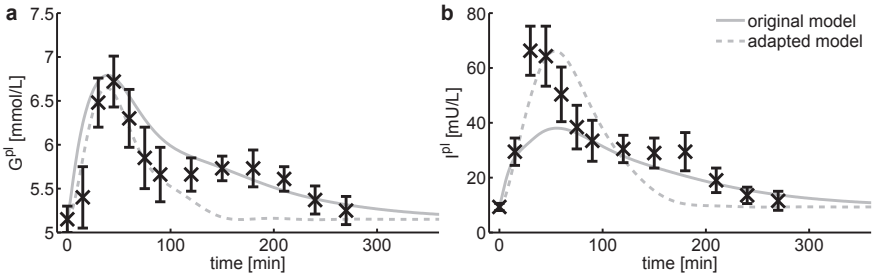

Fig. 6. The physiology-based dynamic model can also describe postprandial profiles for pre-diabetic cases. Panel **a** shows the postprandial glucose level whereas panel **b** describes the postprandial insulin level. The black error bars represent the data by Nazare et al. [38] following a low GI meal in non-diabetic overweight subjects. The solid lines represent the model simulations with the healthy model parameters for beta-cell function and insulin sensitivity. The dashed lines show the model simulations using the adapted model parameters where the insulin sensitivity and beta cell function are re-estimated to describe the pre-diabetic case more closely.

also the variability within the same meal is apparent. A multitude of factors has been identified that attribute to the observed differences in postprandial dynamics between different types of food. Here, we focus on meals that contain starch, of which the digestion and absorption rates of glucose predominantly depend on the accessibility of the starch molecules to the digestive enzymes. Starch encapsulation due to the physical barrier that is formed by lipids, proteins and/or fibers impedes digestion [29,48,49]. Moreover, the microstructure of the food, and especially the porosity of the food, affects starch accessibility as well: more porous foods are digested faster and result in a quicker appearance of exogenous glucose in the plasma [48,50]. Food preparation techniques, such as heating, alter the food's microstructure and may cause a different PPGR than unprocessed foods [48,51]. The nature of the monosaccharide components (glucose vs. fructose or galactose) [52] and the conformation of the starch macromolecules (amylose:amylopectin ratio) [48,49] have also been found to affect the digestive and absorptive processes.

In addition, subject-dependent factors such as the mastication ratio [8] and gastric drainage speed may also contribute to inter-individual differences observed in postprandial responses. Moreover, the degree of insulin sensitivity also contributes to a great extent to the glucose and insulin response dynamics.

Two major contributors to postprandial heterogeneity were taken into account in our PBDM approach: on the one hand the (amount and type of) consumed food itself, and on the other hand the metabolic status of the subject. Whereas existing measures such as GI and GL were found to be inadequate to distinguish between different PPGR kinetics for different foods and do not account for the effects of insulin, our PBDM approach enabled us to take both differences between individuals and differences between meals into account.

4.2. The PBDM provides an accurate description of the postprandial state and accounts for uncertainty in data whilst adhering to physiological constraints

The PBDM we demonstrate in this paper performs well for the large range of postprandial response datasets collected from the literature. We have chosen to use (an extension of) the Eindhoven Diabetes Education Simulator (E-DES) model by Maas et al. [28] because of its physiological description of glucose metabolism. Previously published models of the glucose-insulin system include the Bergman minimal model [53] and the Dalla Man model [54]. Both these models are used for the assessment of insulin sensitivity indices and evaluation of beta-cell function from OGTTs. The model by De Fronzo et al. [17] was developed to analyze glucose clamp studies. In contrast to these generally accepted models, which are typically larger and more detailed, our model is a so-called 'minimal' model with a limited number of parameters that can be estimated from experimental data. Since its underlying equations describe physiology-based processes, we ensured that the simulated fluxes show physiologically correct behavior as well. This can for example be seen in the biphasic behavior in insulin synthesis. These predictions could be validated experimentally (using e.g. tracers [55] or C-peptide measurements), but this is beyond the scope of this paper.

Extending the model may lead to a better comprehension of the physiological processes behind the equations (in modeling referred to as a reduction in model bias). However, having more parameters without additional data would increase model uncertainty (increased variance).

We pursued a model that represents the glucose-insulin regulatory system under everyday life conditions. In contrast to computational models developed under more artificial conditions, our PBDM describes the postprandial response to realistic food products and common composite meals rather than only OGTTs or 'mixed meals' with a very specific composition. Furthermore, our PBDM was made food-specific. Ståhl et al. [56] previously demonstrated a food-specific modeling approach in which differences in digestion rate between different classes of carbohydrates were incorporated. However, we could not adopt this approach, since the exact food composition in terms of rapidly available and slowly available glucose are prerequisites for the Ståhl et al. model. Our food modeling approach does not require any *a priori* information except for the carbohydrate content of the consumed food, and is thereby applicable to study postprandial response kinetics for any food product or mixed meal.

The PBDM uses a relatively simple model for the gastric emptying process, which resembles the physiological response upon carbohydrate ingestion, digestion and absorption in the blood. In this food modeling approach, only four parameters are unknown, yet have shown to be sufficient to describe the

postprandial response for all food types. However, we found that the simulation results highly depend on the rate of appearance (Ra) model. We have shown that the alteration of insulin sensitivity and beta-cell function improves the description of the insulin dynamics, but only to a limited extent. This can be explained from the fact that the model lumps many regulatory effects present in the gastrointestinal tract in a single equation. For example, it does not include Glucagon-like peptide-1 (GLP-1), an incretin hormone that is secreted from the intestine upon food intake and stimulates insulin secretion [57]. Including this effect could yield higher and faster postprandial insulin response profiles. Future work could consider fine-tuning the Ra model, such that the PBDM's fit to experimental or literature data may be improved. Alternatives could be found in Herrero et al. [58] who present a simple, robust method for estimating the glucose rate of appearance from a mixed meal, or exploring the oral glucose absorption model that was included in the glucose-insulin minimal model by Dalla Man et al. [59].

Our PBDM approach provides a framework to systematically analyze the postprandial response dynamics whilst taking into account the uncertainty in the data due to sparse measurements. In general, the glucose level is assessed at a relatively limited number of points in time in the 2 h after food consumption. Therefore, it is uncertain whether the exact timing and height of the postprandial peak have been captured in this sparsely sampled time period. Although an alternative could be found in a continuous glucose monitoring (CGM) setup – yielding a high temporal resolution for PPGR assessment – such biosensors are not available for insulin.

Our model has the flexibility and freedom to fit the postprandial peak in between the provided data points (instead of directly on top of it). Therefore, the model-based approach is less dependent on the (raw) data points themselves than the existing glycemic measures are.

4.3. The PBDM can be adjusted to represent the metabolic status of an individual

Currently we use the PDBM in a population-based manner: the model is able to accurately describe the average postprandial glucose and insulin response among healthy individuals. However, in contrast to other population-based glucose-insulin models, our PBDM allows for a subject-specific framework in which postprandial data can be analyzed in a personalized setting, and could be employed for the use in *in silico* clinical trials with virtual patients [60,61] We have shown that our PBDM can easily be adjusted towards an altered metabolic status. The adjusted model described the postprandial glucose and insulin response data more accurately than the unadjusted (normal glucose tolerant, insulin sensitive) model, allowing for hyperinsulinemia and/or reduced insulin sensitivity.

A similar approach can be carried out if individual data is available. We showed how the model can be tuned towards a state with a reduced insulin sensitivity and/or altered insulin production and secretion. This patient-specific modeling approach will be highly suitable for application in the field of diabetes management.

In addition, the PBDM could be applied in nutrition research to determine kinetic properties for many more foods products and mixed meals common in everyday life. These could be listed in a table comparable to the one by Atkinson [10], providing patients with an easy look-up table for daily use. We propose to use the kinetic properties as an alternative to the AUC. Although these are more complex than the simple one-value AUC(-derived measures), these do provide information on the actual postprandial dynamics and are able to distinguish between different postprandial kinetics.

Although these kinetic properties could be derived directly from the data (as is done when calculating e.g. MISI [19]), this is very sensitive to the sampling times. We therefore advise to not only carefully consider the time intervals with which data is measured, but also to use the PBDM to obtain a more accurate quantification of the full postprandial dynamics, from which the kinetic properties can easily be extracted.

5. Conclusions

We used a model-based approach to quantify the effect of different types of food on the postprandial glucose-insulin dynamics. Postprandial data for a wide variety of food products and mixed meals was collected, which is now publically available (Supplemental Database 1) and provides a valuable resource for future nutrition studies. The physiology-based dynamic model was used to

reconstruct the full postprandial glucose and insulin dynamics from the sparsely measured, heterogeneous data whilst adhering to physiological constraints as embedded in the model equations. This PBDM provided a framework to systematically and accurately analyze postprandial glucose response dynamics by simultaneously taking the insulin response dynamics into account as well. Furthermore, the PBDM can be adjusted to account for the metabolic status of an individual.

Statement of Authorship

YJR, AHM, CvP, WJC, HRH, PAH and NAvR designed the research, YJR conducted the research; YJR, AHM and NAvR analyzed the results; YJR wrote the manuscript; AHM, CvP, WJC, HRH, PAH and NAvR provided critical review; YJR had primary responsibility for the final content. All authors read and approved the final manuscript.

Conflicts of interest

HRH is owner of HRH Diabetes Games B.V. The other authors have no competing interests with regard to this study or the publication of this article.

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List of abbreviations

(2h-i)AUC	(2 h incremental) area under the curve
GI	glycemic index
GL	glycemic load
G^{pl}	plasma glucose concentration
I^{pl}	plasma insulin concentration
OGTT	oral glucose tolerance test
PBDM	physiology-based dynamic model
PPGR	postprandial glycemic response

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.yclnex.2018.01.003.

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