Modeling of postprandial glycemic response by consecutive reaction kinetics model for precise glycemic control

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Abstract

Objective The dynamics of postprandial glycemic response are crucial for human health, while there is currently a lack of efficient models that can capture its fine features.

Methods To address this gap, a physiologically relevant model based on consecutive reaction kinetics (CRK) was developed in this study to describe human postprandial glycemic response dynamics.

Results The model yielded robust fittings for both simulated and experimental glycemic data (comprising 134 datasets), and demonstrated flexibility in capturing the fine features of glycemic responses to a wide range of real foods, such as blood glucose rising and dropping rates.

Conclusion The CRK model developed in this study should be applied in the future together with food and personal information to better understand the determinants of the variance of human postprandial glycemic response dynamics.

Introduction

Being able to precisely characterize and quantify the postprandial glycemic response is crucial in terms of identifying factors that are responsible for individual variation and optimizing diet recommendations to target broader improvements in cardiometabolic health [1]. Currently, fasting blood assays are applied in many clinical diagnoses, such as type 2 diabetes. However, most people are predominantly in their postprandial state during the waking hours. Postprandial hyperglycemia raises the risk of coronary heart disease, cardiovascular disease, and cardiovascular mortality, even in individuals with normal fasting glucose level, highlighting the relevance of diet and its metabolic consequences in cardiovascular risk [2].

Currently, the glycemic index (GI) is the widely used parameter for describing the postprandial glycemic response of carbohydrate-based foods [3]. GI is defined as the ratio of 2-h incremental area under the glycemic curve (iAUC)

after consuming a carbohydrate-based food to that of a reference food by more than 10 healthy individuals (ISO method 26642:2010). Typically, white wheat bread and glucose are used as reference foods, with a GI value of 100. To consider the effects of consumed carbohydrate amount on the postprandial glycemic response, the concept of glycemic load (GL) was introduced [4]. GL is defined as the product of the amount of available carbohydrate (in a specified food consumption size) and GI, which is further divided by 100. Therefore, GL is of advantage compared to GI in terms of reflecting the actual postprandial glycemic response of foods. For instance, watermelon has a high GI value [4], but it is low in carbohydrate content (e.g., ~5 g carbohydrate per 100 g of watermelon). As a result, watermelon would have a small glycemic response.

Despite the widespread use of GI and GL, many criticisms exist regarding their methodology and applicability in improving human health. One of the fundamental issues is the high inter- and intra-individual variance of glycemic responses to foods with the same GI and GL values [5]. For instance, the postprandial glycemic response to the same food or mixed meals can differ substantially among different healthy individuals, possibly due to differences in lifestyle, degree of mastication, insulin sensitivity, and other physiological factors [5–8]. Furthermore, both GI and GL cannot capture the nuances of the postprandial glycemic response dynamics, such as the rate

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of glycemic rise and fall. Some physiology-based mathematical models have been proposed to fit the postprandial glycemic response dynamics and result in physiology-based parameters (e.g., [9]), but these models frequently involve many parameters and may suffer from overfitting issues.

Therefore, the objective of the current study was to develop a mathematical model depending on the consecutive reaction kinetics (CRK) that uses a few parameters to accurately describe the postprandial glycemic response dynamics of various foods. The CRK model was initially validated using manually generated data sets with added experimental noise. Once validated, the model was applied to analyze postprandial glycemic response curves for a broad range of oral glucose tolerance test data sets, as well as foods with different glycemic loads. By applying the newly developed CRK model to these postprandial glycemic response curves, new insights were gained that could be used to develop precise glycemic control strategies in the future.

Methods

Development of the consecutive reaction kinetics (CRK) model

Postprandial glycemic response is a kinetic process, generally consisting of two continuous steps as (1) food digestion in small intestine and glucose entrance to the blood vessel and (2) glucose absorption from blood vessel into tissue cells such as brain, liver, skeletal muscle, and adipose tissue (Fig. 1). Food (normally carbohydrate-based foods) digestion and the absorption of glucose into the blood vessel are the preliminary step, followed by the glucose absorption into tissue cells from the blood vessel [10]. To simplify the mathematical deduction process, each of these two steps was assumed to follow the first-order kinetics, with a characteristic rate constant of k_d (min^{-1}) and k_a (min^{-1}), respectively. Note, both k_d and k_a are defined as the average values for the overall food digestion (first step) and glucose absorption (second step) process instead of any specific process, as each process is consisted of many processes such as the oral

mastication, gastric emptying, and small intestinal digestion, entrance to the hepatic cells from blood vessel. The following equations could then be deduced depending on the rate law.

For the available glucose concentration in the foods:

$$C_F(t) = (C(\infty)) \times \left(e^{-k_d t}\right) \tag{1}$$

For the glucose concentration in the blood vessel:

$$C_B(t) = \frac{k_d \times C(\infty)}{k_a - k_d} \times \left(e^{-k_d t} - e^{-k_a t}\right) \tag{2}$$

For the glucose concentration entering tissues:

$$C_T(t) = C(\infty) \times \left(1 - \frac{k_a \times e^{-k_d t} - k_d \times e^{-k_a t}}{k_a - k_d}\right) \tag{3}$$

In these equations, $C_F(t)$, $C_B(t)$, and $C_T(t)$ are the glucose concentration in food, blood, and tissues at time t (min), respectively, with a unit of mmol/L. $C(\infty)$ (mmol/L) is the maximum glucose concentration entering the tissues after an infinite time. These parameters were determined via the non-linear least squares refinement tool in Excel. The full deduction process of the Eqs. 1–3 was included in the supporting information.

Fitting to the manually produced glycemic data

A series of postprandial glycemic data with experimental noise and different fine features (e.g., peak rising and dropping rate) was manually generated to validate the developed model. The hypothesis is that if the model fitting can produce similar parameters to those applied to generate these artificial data, it suggests that the developed CRK model is a solid procedure to capture the fine details of human postprandial glycemic response dynamics. These parameters to generate the artificial postprandial glycemic data are summarized in Table 1, which were given here as an example and different parameters can also be tested. Twenty-five time points were generated in the range of 0 to 120 min in order to develop high-resolution postprandial glycemic response dynamics. The glucose concentration in the blood vessel

Consecutive reaction model
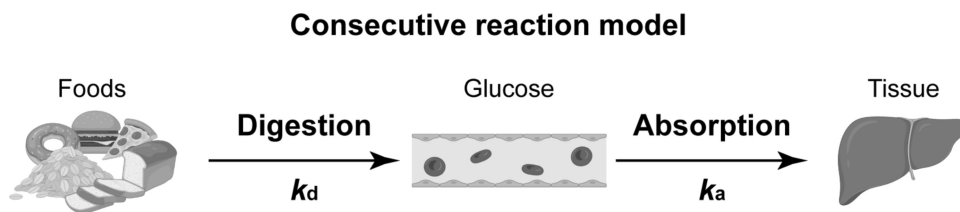
Fig. 1 Schematic diagram showing the consecutive steps of food digestion and glucose absorption. Digestion rate constant is related to many factors such as oral mastication efficiency, gastric empty-ing rate, and intestinal transit time. Similarly, glucose absorption rate constant (from blood vessel to tissues) is controlled by factors such as insulin resistance, activity of glycogen biosynthetic enzymes

Table 1 Artificial parameters applied to generate human postprandial glycemic response curves

Dataset	$C(\infty)$ (mmol/L)	k_a (min^{-1})	k_d (min^{-1})	G_f (mmoL)
1	10	0.05	0.04	5
2	20	0.05	0.04	5
3	10	0.1	0.04	5
4	10	0.05	0.1	5

$C(\infty)$ is the maximum glucose concentration entering the tissues after an infinite time. k_a and k_d are the rate constant for food digestion and glucose absorption, respectively. G_f is the fasting blood glucose concentration

was then produced following Eq. 2. To mimic experimental errors, a series of random numbers within the range of -0.25 to 0.25 were generated via the "RAND" equation and added to the glycemic data in Excel. Each set of artificial data was generated in triplicates. These manually generated data were finally fitted with the developed CRK model via the nonlinear least squares refinement procedure in Excel.

Fitting to oral glucose tolerance test data and foods with a wide range of glycemic load

Oral glucose tolerance test (OGTT) data and postprandial glycemic data of different carbohydrate-containing foods (single or mixed meals) with a wide range of glycemic load from healthy subjects were obtained from the previous publication with permission [9], to further validate the developed CRK model. Generally, OGTT has a simpler glycemic kinetics compared to that for real foods. Datasets were only included when the subjects were identified as healthy and contained > 5 postprandial plasma glucose concentration measurements. Healthy subjects were those with (1) nonpregnant female, (2) stable body weight with no change in dietary habits (3 months prior to the measurements), (3) free of apparent diseases and regular medication, (4) no family history of diabetes and non-obese (i.e., BMI < 30 kg/m^2), (5) normal hemoglobin level with HbA$_{1C}$ < 6.5%, (6) diastolic blood pressure < 80 mmHg and systemic blood pressure < 120 mmHg, and (7) normal glucose tolerance with fasting plasma glucose level < 5.6 mmol/L, 2-h postprandial plasma glucose level < 7.8 mmol/L, and postprandial plasma glucose peak < 11 mmol/L. Only the datasets within 2 h were collected when they only have the glucose rising and dropping period (i.e., without significant drop below the fasting glucose level and then a second rising), as it mainly involves the food digestion and glucose absorption process (other processes such as glycogen degradation are less significant during this period), as shown in Fig. 1. Detailed information for all these datasets is included in the supporting information.

Statistical analysis

The means and standard deviations were determined via Excel.

## Results and discussion

Validation of CRK model

The manually generated glycemic data with the CRK model fitting results are shown in Fig. 2. It shows that CRK model generally gave satisfactory fittings, which could reproduce the whole manually generated glycemic data with $R^2 > 0.97$. Notably, the CRK model demonstrates the ability to capture the fine features of postprandial glycemic response dynamics by modifying the fitting parameters. For example, increasing the k_d from 0.04 to 0.1 resulted in a more rapid increase in glycemic response, while raising the k_a from 0.05 to 0.1 led to a sharper decrease in glycemic response. Additionally, increasing the $C(\infty)$ from 10 to 20 produced a marked increase in the area under the whole curve.

The CRK predicted parameters are given in Table 2. Consistent with Fig. 2, the CRK model produced parameters that were comparable to those employed in the creation of the simulated glycemic data (Tables 1 and 2). This further supports the notion that the developed CRK model was satisfactory in terms of fitting the postprandial glycemic data with the effects from the experimental noise (i.e., the noise introduced through the use of the "RAND" function).

OGTT data fitting

Thirty-four OGTT datasets were collected from thirty-one different publications (references [11–40]), and detailed information on these datasets can be found from the supporting information. Figure 3A illustrates the heterogeneity of the postprandial glycemic response dynamics for these OGTT datasets. Although these postprandial glycemic response profiles may have a comparable 2 h iAUC (i.e., GI = 100 and GL = 75 or 50), they all show distinct dynamics, such as peak height and width. It reinforces the idea, mentioned in the "Introduction" section, that GI or GL cannot fully capture the nuances of various postprandial glycemic response dynamics. In addition, GI and GL measurements are highly dependent on the postprandial glucose sampling interval.

The CRK model developed in this study was employed to fit all 34 OGTT datasets, and an example of such a fitting is shown in Fig. 3B. The fitting parameters for all datasets can be found in the supporting information. The R^2 values for the fittings were generally greater than 0.7, indicating a good agreement between the model and experimental data. As
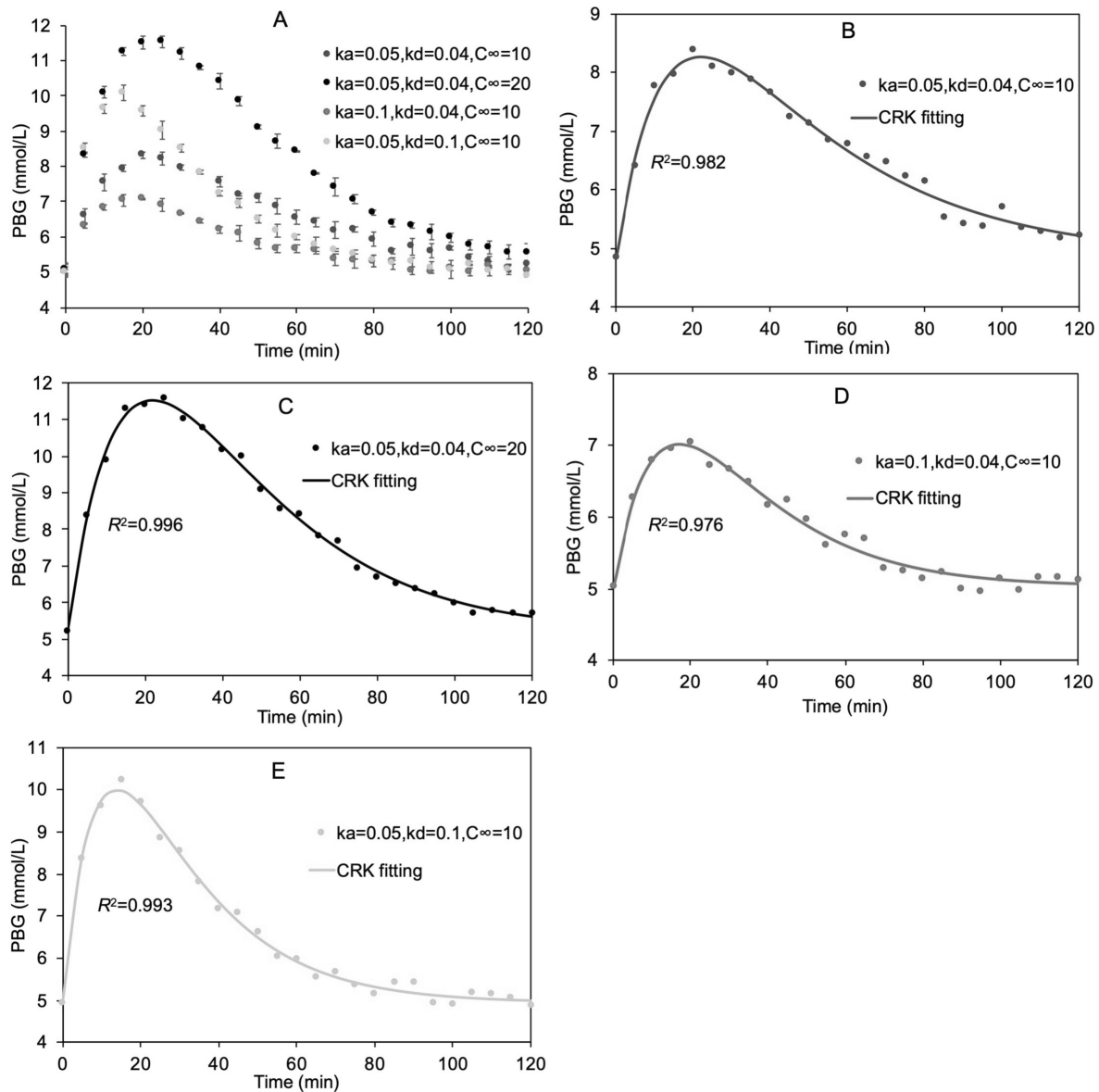
Fig. 2 CRK model fitting for different manually generated postprandial glycemic response dynamics data. These data were generated using Eq. 2 with the parameters summarized in Table 1. CRK is consecutive reaction kinetics. PBG is postprandial blood glucose

seen in Fig. 3A, there were no significant differences observed among the parameters for individuals who consumed 75 g glucose versus those who consumed 50 g glucose. This lack of significant difference could be attributed to the substantial physiological variability among individuals. The majority of k_a values were similar to k_d values, i.e., $k_a/k_d \approx 1$ (Fig. 3C). This outcome is reasonable as in healthy individuals, glucose entering and leaving blood vessels quickly balance out, resulting in an equilibrium (known as glucose homeostasis, which is the maintenance of stable blood glucose levels within a narrow range). This is why it is reasonable to observe that most of the values of k_a and k_d are similar, and their ratio is approximately 1. However, a few datasets exhibited abnormal k_a/k_d

values. The comparison of one of these abnormal datasets to the dataset with $k_a/k_d \approx 1$ is shown in Fig. 3D. As depicted, when k_a was smaller than k_d, it resulted in a much slower decrease in blood glucose levels following the postprandial glycemic peak, suggesting that individuals with abnormal k_a/k_d values might suffer from reduced insulin sensitivity. It is thus proposed here that the k_a/k_d value may serve as an indicator of insulin resistance for clinical applications.

Fitting to foods with different glycemic load (GL)

Although the postprandial glycemic response for an OGTT test has a relatively simple kinetics, postprandial glycemic

Table 2 CRK predicted parameters for different simulated postprandial glycemic response curves

	$C(\infty)$ (mmol/L)	k_a (min^{-1})	k_d (min^{-1})	G_f (mmoL)	R^2
1	11.12 ± 3.84	0.057 ± 0.011	0.038 ± 0.010	5.07 ± 0.20	0.982 ± 0.003
2	18.74 ± 2.40	0.048 ± 0.004	0.043 ± 0.004	5.07 ± 0.16	0.996 ± 0.001
3	7.70 ± 3.97	0.077 ± 0.026	0.052 ± 0.017	5.01 ± 0.13	0.976 ± 0.003
4	9.87 ± 0.60	0.050 ± 0.002	0.102 ± 0.006	5.02 ± 0.07	0.993 ± 0.001

These values were calculated as mean $\pm$ SD of three replicates. $C(\infty)$ is the maximum glucose concentration entering the tissues after an infinite time. k_d and k_a are the rate constant for food digestion and glucose absorption, respectively. G_f is the fasting blood glucose concentration

response dynamics for real foods are much more complex. The primary biological factors that determine the food digestion process include oral salivation and mastication, gastric motility and emptying, small intestinal motility and enzymes, large intestinal food-microbiota interactions, and gut-brain feedback regulation [10]. Therefore, various foods with a wide range of GL (100 datasets from 23 publications) were further applied to confirm the validity of the developed CRK model [32–58]. Detailed information regarding these datasets can be found in the supporting information. Consistent with the OGTT data shown in Fig. 3A, a high heterogeneity in the postprandial glycemic response, such as peak

height and width, was observed for these foods with different GL (Fig. 4A). Foods with similar GI or GL can also show distinct postprandial glycemic responses, indicating that the GI or GL fails to capture the fine features of the postprandial glycemic response dynamics.

An example of the CRK model fittings for different foods is shown in Fig. 4B, and all the fitting parameters are summarized in the supporting information. Although the CRK model for real foods showed less satisfactory fittings compared to that for OGTT data, most of the fittings can still reproduce the experimental data with an $R^2 > 0.7$. This is reasonable since the digestion of real foods is much more complex than glucose (as
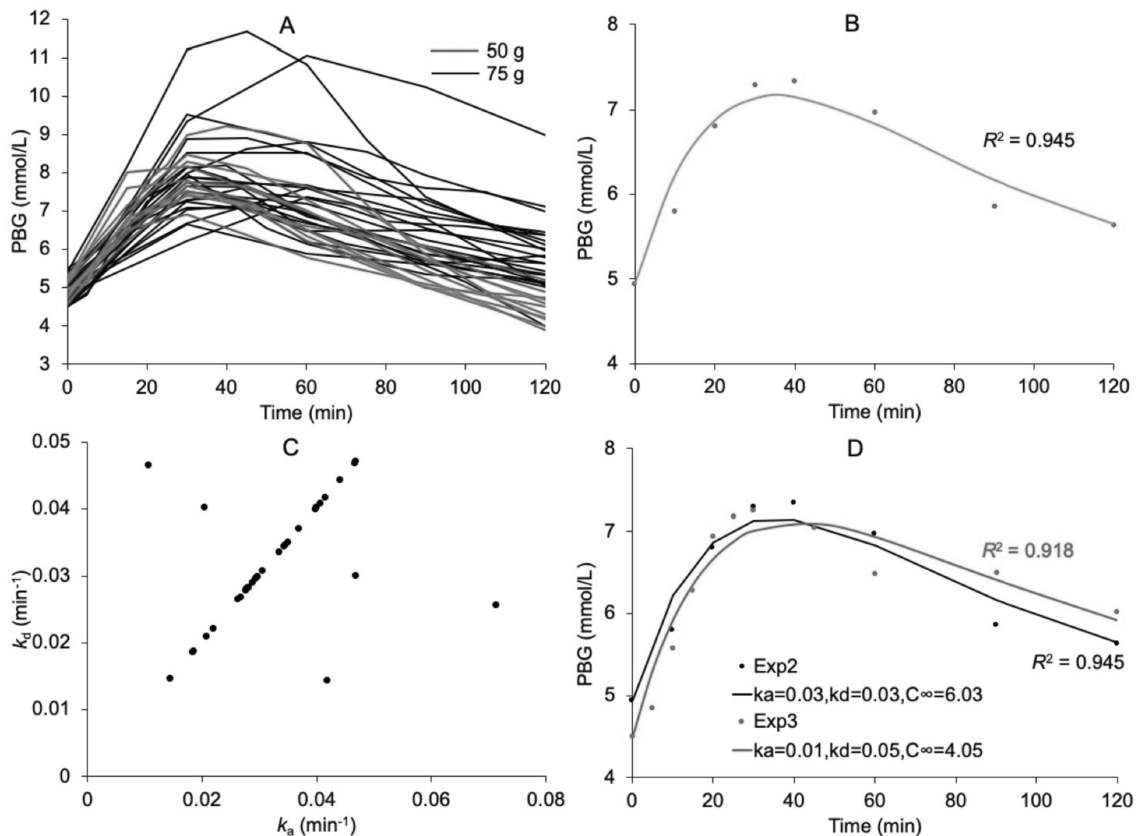
Fig. 3 OGTT datasets (**A**), an example of CRK model fitting to the OGTT data (**B**), comparison of k_a and k_d values (**C**), and comparison between datasets with abnormal k_a/k_d values and $k_a/k_d \approx 1$ (**D**). PBG is postprandial blood glucose. Exp2 and Exp3 are two datasets
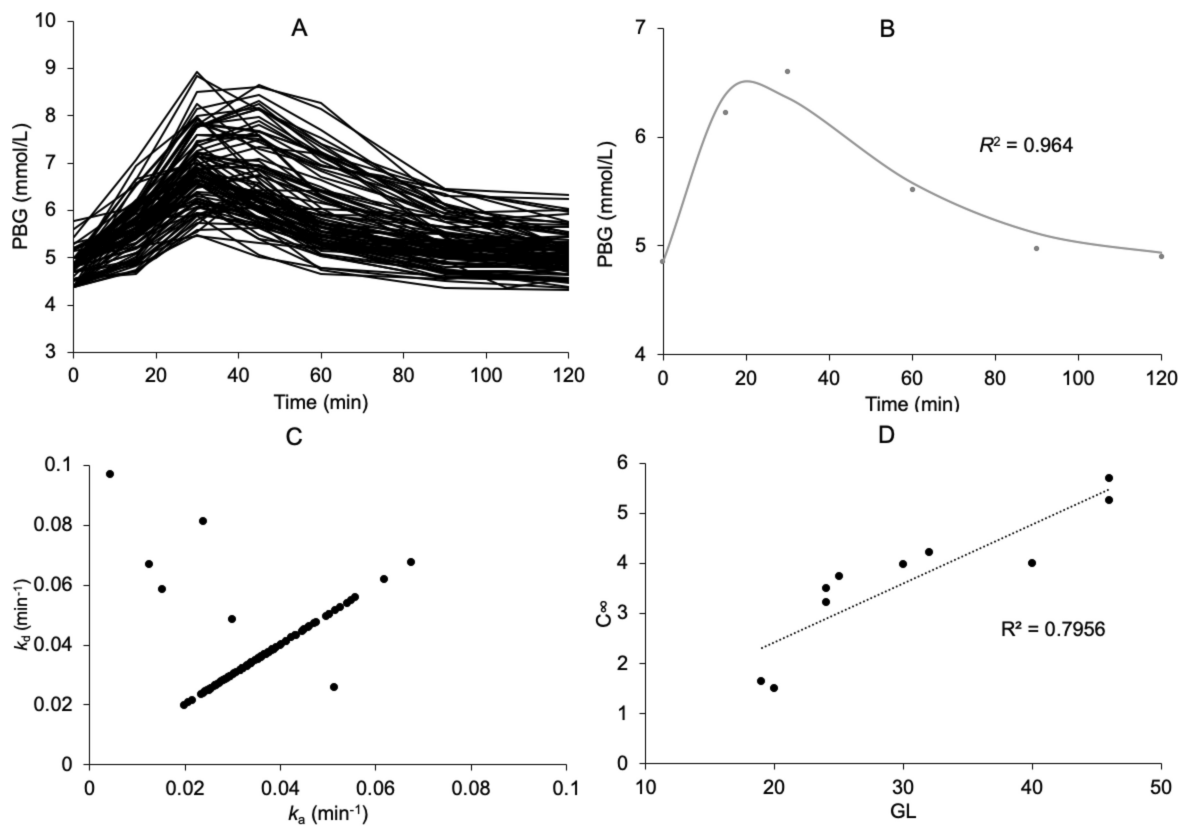
Fig. 4 Postprandial glycemic response dynamics for foods with different GL (**A**), an example of the CRK model fitting (**B**), comparison of k_a and k_d values for these foods (**C**), and relations between GL and $C(\infty)$ for these datasets collected from Ranawana et al. [37] (**D**). PBG is the postprandial blood glucose

mentioned above), which involves many factors from the oral, gastric, and intestinal digestion phase [10]. Therefore, more parameters inherent to the food digestion process might need to be included in the current CRK model in the future to better fit the postprandial glycemic response dynamics of real foods. These factors could include the type and amount of carbohydrates, fiber, fat, and protein, as well as individual differences in gut microbiota, metabolic rate, and insulin sensitivity [59, 60]. Nevertheless, the developed CRK model is generally flexible in fitting the postprandial glycemic response kinetics for a wide variety of real foods (i.e., $R^2 > 0.7$). Consistent with the OGTT data, most of the k_a/k_d values were close to 1 (Fig. 4C), supporting the validity of k_a/k_d value as an indicator of insulin resistance. It is often assumed that the GI of a food is determined solely by the food digestion rate or the glucose absorption rate into tissues. However, GI values from different foods did not show significant correlations with either k_a or k_d values, suggesting that GI of food does not solely depend on the food digestion rate or the glucose absorption rate into tissues. This finding highlights the need for a more comprehensive understanding of the factors that contribute to the GI of a food. Although the GL values showed less correlation with the $C(\infty)$ values for all the 100 datasets, their linear correlations were much clearer when plotted from the same study (e.g., Fig. 4D). It suggests that the GI and GL values obtained from different studies might not be suitable for comparison. On the other hand, it supports the validity of the developed CRK model, as a higher glucose load would result in a greater amount of glucose entering the tissues in healthy subjects.

Conclusions

In this study, a mathematical model depending on the consecutive reaction kinetics was developed to accurately describe and capture the complex dynamics of human postprandial glycemic response. Key findings from this study include as follows: (1) the developed CRK model was able to capture features such as the rising and falling rates of blood glucose, and was validated using both manually generated and previously published experimental data, although the model fit better to oral glucose tolerance test data compared to those for real foods; (2) by applying the CRK model to the actual experimental data, it suggested that the ratio of k_a/k_d could be an indicator of insulin resistance, with healthy individuals generally having equal k_a and k_d values.

This model has a wide range of potential applications in the field of nutrition and health. Personalized nutrition plans based on an individual's unique physiological characteristics can be developed by using the CRK model to gain a better understanding of the factors that impact postprandial glycemic response. In addition, food manufacturers can use the model to design products that have a lower glycemic response, which could be beneficial for people who are trying to control their blood sugar levels. In terms of clinical research, the model can be used to design and analyze clinical trials that investigate the effects of various interventions such as drugs, supplements, or lifestyle changes on postprandial glycemic response. Finally, this model could be used to help people with diabetes better manage their blood sugar levels by predicting how different foods and interventions will affect their glycemic response. Overall, the CRK model developed in this study has significant potential to improve our understanding of the complex dynamics of postprandial glycemic response and to inform interventions for the prevention and management of chronic diseases such as type 2 diabetes.

Declarations

Conflict of interest The author declares no competing interests.

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