Toward Better Understanding of Insulin Therapy by Translation of a PK-PD Model to Visualize Insulin and Glucose Action Profiles

Karen Schneck, PharmD¹, Lai San Tham, PharmD², Ali Ertekin, MD³, and Jesus Reviriego, MD, PhD⁴

Abstract

Insulin replacement therapy is a fundamental treatment for glycemic control for managing diabetes. The engineering of insulin analogues has focused on providing formulations with action profiles that mimic as closely as possible the pattern of physiological insulin secretion that normally occurs in healthy individuals without diabetes. Hence, it may be helpful to practitioners to visualize insulin concentration profiles and associated glucose action profiles. Expanding on a previous analysis that established a pharmacokinetic (PK) model to describe typical profiles of insulin concentration over time following subcutaneous administration of various insulin formulations, the goal of the current analysis was to link the PK model to an integrated glucose-insulin (IGI) systems pharmacology model. After the pharmacokinetic-pharmacodynamic (PK-PD) model was qualified by comparing model predictions with clinical observations, it was used to project insulin (PK) and glucose (PD) profiles of common insulin regimens and dosing scenarios. The application of the PK-PD model to clinical scenarios was further explored by incorporating the impact of several hypothetical factors together, such as changing the timing or frequency of administration in a multiple-dosing regimen over the course of a day, administration of more than 1 insulin formulation, or insulin dosing adjusted for carbohydrates in meals. Visualizations of insulin and glucose profiles for commonly prescribed regimens could be rapidly generated by implementing the linked subcutaneous insulin PK-IGI model using the R statistical program (version 3.4.4) and a contemporary web-based interface, which could enhance clinical education on glycemic control with insulin therapy.

Keywords

insulin, modeling, pharmacodynamics, pharmacokinetics, simulation

An estimated 425 million people worldwide are currently living with diabetes, and by 2045, that number is expected to increase to 629 million.¹ Insulin replacement has been a crucial treatment for people with type 1 diabetes mellitus (T1DM) and an important adjunctive pharmacotherapy option for people with type 2 diabetes mellitus (T2DM).²³ An understanding of the impact of insulin use on blood glucose is essential because seminal studies, such as the Diabetes Control and Complications Trial⁴ and the United Kingdom Prospective Diabetes Study,⁵ have shown the significant bearing of glycemic control on the burden of diabetes.

The development of commercial insulin preparations has undergone many advances over the past century.⁶ The engineering of insulin analogues has focused on providing formulations with action profiles that mimic as closely as possible the pattern of physiological insulin secretion that normally occurs in healthy individuals without diabetes. To mimic the secretion and behavior of endogenous insulin and to reach optimal therapeutic effectiveness, subcutaneously administered insulin should cause higher insulin concentration when blood glucose is elevated at mealtimes (ie, covering postprandial needs) and lower insulin concentration between meals and during nighttime (ie, covering basal needs).⁷ An intermediate- or long-acting insulin with duration of activity that lasts at least 12 to 24 hours is often prescribed for basal insulin requirements and is commonly used in combination with a rapid-onset, short-acting insulin that has duration of activity ranging from 4 to 6 hours to cover the prandial period.⁶ Commercially available insulin products can be administered in combination, allowing appropriate flexibility in scheduling dosing times (eg, long- or intermediate-acting insulin taken at bedtime with rapid- or short-acting insulin taken prior to meals).

¹Eli Lilly and Company, Indianapolis, IN, USA
²Lilly Center for Clinical Pharmacology Pte Ltd, Singapore
³Eli Lilly and Company, Istanbul, Turkey
⁴Eli Lilly and Company, Madrid, Spain

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Corresponding Author:
Karen Schneck, PharmD, Global PK/PD & Pharmacometrics, Eli Lilly and Company, Indianapolis, IN 46285
Email: kschneck@lilly.com
Whenever patient conditions are considered appropriate, the number of injections may be reduced by using premixed formulations, which combine intermediate-acting insulin, such as isophane insulin or insulin lispro protamine suspension (ILPS), and rapid-acting insulin, such as insulin lispro, to be delivered as a single injection.8,9 Because of the availability of a wide variety of insulin treatment options, a tool that enables the visualization of the time course of insulin concentrations and the associated glucose action profiles may be helpful to health care practitioners.

Expanding on a previous analysis that established a pharmacokinetic (PK) model to describe typical profiles of insulin concentration over time following subcutaneous administration of various insulin formulations,10 the goal of the current analysis was to link the PK model for subcutaneous insulins to an integrated glucose-insulin (IGI) systems pharmacology model.11–16 Although several pharmacology models describing the feedback relationship between insulin and glucose have been developed over the years,17 the selected glucose-insulin model for this work had a structure that was amenable to joining with the subcutaneous insulin PK model, enabled prospective simulations, and allowed for consideration of population variability. The subsequent linked pharmacokinetic-pharmacodynamic (PK-PD) model was then used to simulate insulin concentrations and associated blood glucose response following some commonly prescribed insulin-dosing regimens. The application of the PK-PD model to clinical scenarios was further explored by incorporating the impact of several hypothetical factors together, such as changing the timing or frequency of subcutaneous insulin administration in a multiple-dosing regimen over the course of a day, administration of more than 1 insulin formulation, or insulin dosing adjusted for carbohydrates from meals.

### Methods

#### Clinical Studies

Data from 4 clinical studies, of which 3 were published,18–20 were used to calibrate and qualify the PK-PD model (Table 1). Studies were conducted according to the Declaration of Helsinki, and all subjects provided written informed consent. Studies were focused on either patients with T1DM or patients with T2DM who ingested food after administration of subcutaneous insulin. The insulin formulations investigated in the studies were human regular U-100 insulin (100 U/mL, U-100R, HumulinR U-100), human regular U-500 insulin (500 U/mL, U-500R, HumulinR U-500), premixed human insulin isophane suspension and human regular insulin (100 U/mL, Mix 70/30, Humulin 70/30 U-100), insulin lispro (100 U/mL, IL100, Humalog U-100), premixed ILPS and lispro insulin (100 U/mL, Mix 75/25, Humalog 75/25 U-100), and insulin glargine (100 U/mL, glargine, Lantus).

During the studies with patients with T1DM (Table 1), patients were fasted for a minimum of 14 hours after receiving their evening dose of NPH.18 Patients using insulin pumps discontinued their basal infusion 2 hours prior to the beginning of the experimental period.18 At the study site, patients began receiving a human regular U-100 insulin infusion intravenously, with the infusion adjusted to maintain a blood glucose concentration of $135 \pm 15$ mg/dL for at least 1 hour prior to the study insulin, and the insulin infusion was discontinued 15 minutes following the injection of the study insulin.18 This procedure to normalize baseline glucose was repeated at the start of each study period. Subjects were administered a single dose of subcutaneous insulin at each testing occasion, and if a study involved more than 1 administration (ie, crossover study design), an adequate duration in the form of a washout period was ensured between doses to preclude carryover concentration effects between study periods for the exogenous insulin(s).18 After subcutaneous insulin administration, a standard test meal of 770 kcal, consisting of approximately 57% carbohydrate (110 g), 14% protein, and 29% fat, was provided by the study site.18 During the study with insulin U-500R,19 insulin treatment was stabilized over 24 weeks in patients with T2DM, and U-500R was administered subcutaneously prior to a standard morning meal containing 374 kcal, consisting of 75 g of carbohydrate.

### Table 1. Insulin Clinical Studies Used for PK-PD Model Calibration and Summary of Subject Demographics (Mean [Range])

| Insulin Formulation | Reference | Subjects (n) | Age (Years) | Dose* (U) | Body Weight (kg) | BMI (kg/m²) | Available Data |
|---------------------|-----------|--------------|-------------|----------|------------------|-------------|----------------|
| Lispro, Regular U-100 | Data on file, 18 | T1DM (31) | 37.2 (23.5–55.4) | 14.8 (10–22) | 73.9 (58.0–93.7) | 24.4 (20.8–30.0) | PK (insulin), PD (glucose) |
| Mix 75/25, Mix 70/30 | Data on file | T1DM (31) | 32.5 (23.5–55.4) | 21.2 (10–38) | 61.6 (41.0–86.0) | 22.6 (—) | PK (insulin), PD (glucose) |
| Regular U-500 | Data on file, 19 | T2DM (22) | 54.0 (40.0–65.0) | 149 a (87–302) | 114 (64–154) | 38.8 (27.5–52.7) | PD (glucose) |
| Glargine | 20 | T2DM (20) | 53.5 b (10.7) | 44 (14–100) | 108 b (25.7) | 36.7 b (8.6) | PD (glucose) |

BMI, body mass index; Lispro, insulin lispro; Mix 75/25, premixed 75% insulin lispro protamine suspension and 25% insulin lispro; Mix 70/30, premixed 70% isophane insulin suspension and 30% human regular insulin; n, number of subjects; PD, pharmacodynamic; PK, pharmacokinetic; Regular U-100, human regular insulin 100 U/mL; Regular U-500, human regular insulin 500 U/mL; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; U, units.

aThe insulin dose administered prior to the study meal or at bedtime for glargine.
20 g of protein, and 3.5 g of fat. Treatment with insulin glargine was adjusted and stabilized over 24 weeks, after which patients with T2DM were admitted to a study site and observed for a 24-hour period. Insulin glargine was administered subcutaneously at bedtime and individualized total caloric intake was calculated using the Harris-Benedict equation and was divided over 3 meals, with each meal consisting of approximately 50% carbohydrate, 20% protein, and 30% fat.

Blood samples for the determination of glucose and serum immunoreactive insulin concentrations, if specified in the study protocol, were collected frequently at intervals covering the duration of meal(s). Plasma glucose concentrations were measured by a central laboratory using standard assays. Total (bound and unbound) insulin concentrations were determined by validated radioimmunoassays that were commercially available at the time the study was conducted. Insulin concentrations collected from patients with T1DM were assumed to reflect the subcutaneous insulin administered because inclusion criteria for study participation stipulated that patients have a fasting C-peptide concentration of < 0.9 ng/mL. The discrimination between insulin derived from subcutaneous insulin administration and endogenously secreted insulin in healthy volunteers or patients with T2DM to determine subcutaneous insulin PK has been discussed previously.

Insulin PK Model Linked to IGI Model

A PK model to describe insulin concentrations following subcutaneous administration of various insulin formulations was previously developed and validated. The PK model structure (Figure 1) was based on the assumption that absorption behavior differs between the different formulations of the same insulin type. The insulin types were categorized as regular, lispro, or glargine insulin. After absorption, the distribution and elimination behaviors are the same for the same type of insulin. Hence, the insulin PK was best described by a PK model that was parameterized by a distinct absorption rate constant (ka) for each formulation and an apparent volume of distribution (Vd/F) for each insulin type. Body weight was a significant covariate on Vd/F for regular insulin, insulin lispro, and insulin glargine. The bioavailability parameter for insulin glargine, the ka of regular insulin, and the CL/F for regular insulin showed a relationship with the administered dose amount.

A published IGI systems pharmacology model (supplementary equations 1–13) was used to characterize the blood glucose response following subcutaneous insulin administration (Figure 1). The key components of the glucose and insulin feedback system are briefly summarized in this section. The model parameterizations for oral intake of glucose from a meal were explored in this analysis using a single first-order absorption rate constant and, second, a more
mechanistic representation of the gastrointestinal tract. The mechanistic gastrointestinal tract approach describes gastric emptying of glucose from the stomach to the small intestine. Glucose absorption is parameterized as the sum of nonlinear functions from the small intestine, which comprises 3 compartments (duodenum, jejunum, and ileum), to the central glucose distribution compartment (supplementary equation 13). Carbohydrates from meals can be introduced to the system by converting the carbohydrates in units of kilocalories to grams of glucose input through the conversion factor of 4 kcal of carbohydrate per 1 g of glucose. Systemic glucose disperses into a central and a peripheral distribution area. The movement of glucose in the system is parameterized in terms of clearance for either elimination or movement between compartments, and the clearance terms translate to rate parameters by incorporating estimated volumes of distribution for compartments. Elimination of glucose from the system is represented by 2 pathways: clearance of glucose independent of the influence of insulin (CLG, I) and clearance of glucose affected by insulin (CLGI). The model has a baseline secretion of insulin, representing pancreatic release of insulin, and clearance of insulin from a central insulin compartment (CLI), representing insulin elimination from the plasma. The endogenous pancreatic secretion of insulin is stimulated by elevated glucose amounts and has a nighttime decrease of insulin secretion. First-order rate constants between the central compartments and the effect compartments were used to capture the delays in the effects of glucose and insulin. The volumes for the glucose distribution compartments and the endogenous insulin distribution compartments are scaled by body weight.

The PK model was integrated with the IGI model by linking exogenous insulin concentrations to the clearance of glucose affected by endogenous insulin (CLGI). The endogenous insulin secretion from the pancreas for patients with T2DM was assumed to be approximated by the steady-state insulin concentration (ISS) reported in literature for patients with T2DM approximated by the steady-state insulin concentration (ISS) reported in literature for patients with T2DM was assumed to be

| Parameter (Unit) | Typical Value | Reference |
|------------------|---------------|-----------|
| Glucose absorption |               |           |
| $k_w$ (1/min)    | 0.14          | 16        |
| $\mathrm{GSS}_{\mathrm{HV}}$ (g) | 7.42          | 16        |
| $\gamma$ (--)    | 14            | 16        |
| $\mathrm{RA}_{\text{max D}}$ (g/min) | 0.58          | 16        |
| $\mathrm{RA}_{\text{max J}}$ (g/min) | 2.06          | 16        |
| $\mathrm{RA}_{\text{max I}}$ (g/min) | 1.33          | 16        |
| $\mathrm{K}_{\text{ss}}$ (g) | 6.32          | 16        |
| $\mathrm{k_{aG}}$ (1/min) | 0.0151       | 14        |
| Glucose disposition |             |           |
| $\mathrm{CG}$ (L) | 9.33          | 11,12,14,16 |
| $\mathrm{CG}$ (L) | 8.56          | 11,12,14,16 |
| $\mathrm{CL}_{\text{GI}, \text{HV}}$ (L/min) | 0.0894       | 12        |
| $\mathrm{CLI}$ (L/min) | 0.0287        | 11,12,14,16 |
| $\mathrm{CL}_{\text{GI}, P}$ (L/min) | 0.00829, 0.0066 | 12, 16    |
| $\mathrm{CL}_{\text{GI}, H}$ (L/min)$^2$ | 0.00074, 0.0055 | 14, 16    |
| $\mathrm{Q}_{\mathrm{G}}$ (L/min) | 0.442         | 11,12,14,16 |
| $\mathrm{k}_{\text{CE}}$ (1/min) | 0.012, 0.0573 | 14, 16    |
| $\mathrm{S}_{\text{max}}$ (fraction/mg) | 0.000994      | 14        |
| $\mathrm{GSS}_{\text{HV}}$ (mg/dL) | 95.4          | 16        |
| $\mathrm{GSS}_{\text{PAT}}$ (mg/dL) | 158, 135      | 14, 16    |
| Endogenous insulin disposition |             |           |
| $\mathrm{CV}$ (L) | 6.09          | 11,12,14,16 |
| $\mathrm{C_{L}}$ (L/min) | 1.22         | 11,12,14,16 |
| $\mathrm{k}_{\text{IE}}$ (1/min) | 0.00773      | 14        |
| $\mathrm{IPRG}$ (--) | 1.42          | 11,12,14,16 |
| ISS (mU/L) | 10            | 14        |

$\mathrm{CV}$, pancreatic insulin clearance; $k_w$, rate constant for the insulin effect compartment linked to insulin-dependent glucose clearance; $\mathrm{CL}_{\text{GI}, \text{HV}}$, insulin-independent glucose clearance for healthy volunteers; $\mathrm{CL}_{\text{GI}, P}$, insulin-dependent glucose clearance for patients with type 2 diabetes mellitus; $\mathrm{CL}_{\text{GI}, H}$, insulin-dependent glucose clearance for healthy volunteers; $\mathrm{CL}_{\text{GI}, P}$, insulin-dependent glucose clearance for patients with type 2 diabetes mellitus; $\mathrm{GSS}_{\text{HV}}$, glucose baseline concentration at steady state for healthy volunteers; $\mathrm{GSS}_{\text{PAT}}$, glucose baseline concentration at steady state for patients with type 2 diabetes mellitus; $\mathrm{GSS}_{\text{HV}}$, glucose amount giving 50% inhibition of gastric emptying; $\mathrm{IPRG}$, control parameter for the glucose effect on insulin secretion; ISS, pancreatic insulin baseline concentration at steady state; $k_{aG}$, first-order absorption rate constant of glucose; $k_{GE}$, rate constant for the glucose effect compartment linked to insulin secretion; $K_{\text{ss}}$, amount of glucose giving 50% of maximum absorption; $k_{\text{ss}}$, gastric emptying rate for noncaloric liquid; $QG$, intercompartmental clearance of glucose; $S_{\text{max}}$, shape parameter for gastric inhibition of glucose emptying.

The differential equations from the linked insulin PK and IGI model were first implemented using the differential equation solver RxODE in the R statistical program (version 3.4.4) to estimate fixed and random effects potentially sensitive to drug intervention or study typical mean insulin and glucose concentrations for comparison with mean observed data. This approach was a convenient means of quickly exploring the adequacy of the previously published parameter estimates (Table 2) and the proposed model structure for the relationship between PK and IGI models.

The PK and IGI models were implemented in a nonlinear mixed-effects modeling program (NONMEM version 7.4) to estimate fixed and random effects.
population. The sequential approach to population PK-PD analysis\textsuperscript{25} was employed, wherein the PK model parameters were fixed in the linked PK-IGI model during exploratory calibration of the IGI model parameters.

The model parameter estimates from the NONMEM analyses were then used with the R program (version 3.4.4) to simulate insulin and glucose time courses. After the PK-IGI model was qualified against observed data, the model was translated to the R web-browser toolkit package, Shiny\textsuperscript{26,27} which enabled the construction of a dashboard-like user interface that allowed interactive user control for input of initial conditions and subsequent visualization of the simulation outputs, which include both mean subcutaneous insulin PK and glucose profiles.

**Results**

**Insulin PK-IGI Model Calibration**

Published parameter estimates\textsuperscript{10–16} were used in the PK-IGI model differential equations to simulate profiles of insulin concentration and blood glucose over time, and these profiles approximated the shape of observed insulin and glucose profiles. By visual inspection, the simulated mean profile of insulin concentration over time generally followed a mean trend through observed insulin data from clinical studies. The simulated mean glucose-over-time profile was noticeably divergent from clinical postprandial glucose observations (Supplementary Figure S1). These initial findings suggested the linked PK-IGI model structure was a reasonable base model, but there were some deficiencies that required closer examination of the parameters and model structure.

Although the simulated insulin concentrations using the insulin PK parameters from the previous analyses overlaid the observed data, population PK analysis was conducted on U-100R and insulin lispro data collected from patients with T1DM to confirm that the estimated PK parameters were consistent with historical analyses. The PK parameter estimates for U-100R (\(k_{a}, 0.59\) L/h; \(CL/F, 99.3\) L/h; \(V_d/F, 146\) L) for patients with T1DM were comparable to the estimates reported for healthy volunteers (\(k_{a}, 0.67\) L/h; \(CL/F, 127\) L/h; \(V_d/F, 178\) L).\textsuperscript{10} The estimated PK for insulin lispro (\(k_{a}, 0.765; CL/F, 66.6\) L/h; \(V_d/F, 54.1\) L) in patients with T1DM were also consistent with the estimates from healthy volunteer data (\(k_{a}, 0.989\) L/h; \(CL/F, 30.5\) L/h; \(V_d/F, 43\) L).\textsuperscript{10} The similarity of subcutaneous insulin PK in healthy volunteers, patients with T1DM, and patients with T2DM, after accounting for patient factors such as body weight and dose amount, was consistent with the previous PK model validation.\textsuperscript{10}

The insulin-dependent clearance parameter for glucose (\(CL_{GI}\)) for patients with T1DM has not been previously described in the literature. In patients with T1DM, the parameter \(CL_{GI}\) reflects the effect of exogenous insulin on glucose because insulin production was assumed to be absent in this population. A clinical study that compared postprandial glucose control following subcutaneous administration of regular human insulin, insulin lispro, and ILPS in patients with T1DM was used to estimate \(CL_{GI}\) either simultaneously with \(CL_{G}\) estimation or while \(CL_{G}\) was fixed to a published value. In both cases, the estimates of \(CL_{GI}\) (0.0014–0.0023 [L/h]/[mU/L]) were lower than the value reported for healthy volunteers and patients with T2DM (Table 2). The lower estimated values of \(CL_{GI}\) for patients with T1DM given exogenous insulin suggested an adjustment scalar (values ranging from 0.3 to 0.65) for the exogenous insulin effect relative to the effect of endogenous insulin may be applied to correct for a physiological process unaccounted for in the IGI model, such as the hepatic extraction of pancreatic insulin.\textsuperscript{13,28} In subsequent simulations for patients with T1DM, \(CL_{GI}\) was fixed to the value reported for T2DM, and the fractional scalar parameter was applied to the exogenous insulin concentrations in the compartment for insulin effect on \(CL_{GI}\). When simulating the administration of exogenous insulin to patients with T2DM, the simple addition of exogenous insulin concentrations to endogenous insulin concentrations for the effect on insulin-dependent clearance of glucose overestimated the dampening effect of insulin on blood glucose. Similar to the approach for patients with T1DM, to adjust the effect of exogenous insulin relative to endogenous insulin, a fractional scalar parameter was applied to exogenous insulin concentrations in the insulin effect compartment linked to \(CL_{GI}\).

The impact of the ingestion of carbohydrates was explored with 2 model structures. The simple approach used a single first-order absorption rate constant to describe movement from a carbohydrate depot compartment to the central glucose compartment, whereas a mechanistic approach to glucose absorption involved compartments representing the small intestine (Supplementary Equations 12 and 13). The potential impact of the glucose absorption model structure was explored through simulations in the R program. The estimated value (0.0061/min) for the first-order absorption rate for glucose (\(k_{aG}\)) was lower than the published value (Table 2). For the simulations using the mechanistic absorption model, the parameters for small intestine transit time were fixed to published values,\textsuperscript{16} and glucose input from a meal was split into fractions and had input times assigned manually to mimic pulsatile gastric emptying. The fraction of total glucose, number of glucose input times, and interval between the glucose input times were tested by directly coding into the
Figure 2. Simulated insulin concentration and blood glucose over time compared with study observations in patients with T1DM administered a meal and (A1, B1) U-100R, (A2, B2) Mix 70/30, (A3, B3) insulin lispro, or (A4, B4) Mix 75/25. The solid red line represents the simulation mean, the solid blue line represents the mean of the observations, and open circles represent actual individual observations from studies (Table 1). FRI, free immunoreactive insulin; Mix 70/30, premixed 70% isophane insulin suspension and 30% human regular insulin; Mix 75/25, premixed 75% insulin lispro protamine suspension and 25% insulin lispro.

R program and visually inspecting for closeness of the simulation curves to the mean observed data for each type of insulin (Figure 2). It was noted that the use of a mechanistic glucose absorption model with transit compartments and pulsatile input of glucose gave the most flexibility to fit diverse glucose absorption patterns. The ability to adjust glucose absorption lag and rate may lead to improved simulations that reflect real-world conditions because the composition of a meal can affect the shape of the glucose response curve over time.29

When incorporating the changes described above, the resulting insulin concentration and glucose-over-time simulations from the linked subcutaneous insulin PK-IGI model compared well with observed data for each insulin formulation (Figures 2 and 3), and the linked subcutaneous insulin PK-IGI model was implemented on an interactive web interface display (Supplementary Figure S2). Exploring glucose absorption models with different levels of complexity permitted adequate fitting of observed glucose data from multiple studies that used various subcutaneous insulin types.
administered with meals of varying composition. Understanding the contribution of subcutaneous insulin PK and the influence of meal-related factors (eg, nutrient composition, meal duration) on blood glucose response may lead to improved prediction of real-world scenarios.

Simulations of Clinical Scenarios
Typical mean insulin concentrations and blood glucose over time were simulated for illustrative examples of some key concepts for insulin replacement therapy.

**Example 1.** Patients with T2DM may benefit from insulin treatment because of decreased capacity to secrete insulin and increased requirement for insulin to overcome resistance to the insulin effect on glucose. In Figure 4, a simulation of 1 example profile of uncontrolled blood glucose in a patient with T2DM is presented. In this scenario, the hypothetical patient is assumed to weigh 85 kg and consume approximately 30 kcal/kg/day over 3 meals, with the evening meal slightly larger than the other meals, and carbohydrates contribute approximately 50%-60% of the total kilocalories of each meal. The assumed hypothetical circumstances are only one of many possible scenarios, and these conditions could be modified to represent individuals with different characteristics. The simulated blood glucose profile of the hypothetical patient with T2DM in this example without treatment with subcutaneous insulin displays elevated glucose (>126 mg/dL).
Figure 4. Simulated blood glucose over time for patients with T2DM without insulin treatment compared with subcutaneous insulin treatment with (A) insulin glargine at bedtime, (B) insulin lispro prior to dinner and insulin glargine at bedtime, (C) insulin lispro prior to breakfast, lunch, and dinner and insulin glargine at bedtime, and (D) Mix 75/25 prior to breakfast and dinner or Mix 50/50 prior to breakfast, lunch, and dinner. The shaded area represents the target glucose range over a 24-hour period. The hypothetical patient conditions assumed for the simulation include body weight of 85 kg and caloric intake of 30 kcal/kg/day, with 50%–60% of calories derived from carbohydrates. A, AM; MN, midnight; Mix 75/25, premixed 75% insulin lispro protamine suspension and 25% insulin lispro; Mix 50/50, premixed 50% insulin lispro protamine suspension and 50% insulin lispro; P, PM.

Between meals and during the sleep period and elevated glucose (≥200 mg/dL) during the postmeal periods. Over a 24-hour period, the estimated average glucose (eAG) is 184 mg/dL, which translates to a glycated hemoglobin (HbA1c) of 8%. An intermediate-acting insulin (such as ILPS) or a long-acting insulin (such as insulin glargine) provides basal coverage by suppressing hepatic glucose production between meals and during sleep at nighttime. With insulin glargine 0.2 U/kg given at bedtime, the simulated fasting plasma glucose, which is the glucose prior to the morning meal, improved and the eAG and HbA1c decreased to 157 mg/dL and 7.1%, respectively (Figure 4A). Patients with T2DM may have deficient and delayed insulin release following meals, resulting in high postprandial glucose. Rapid-acting insulins suppress hepatic glucose production and enhance peripheral glucose uptake during the postprandial period. In the simulation, intensifying therapy was explored by adding mealtime insulin to the bedtime insulin glargine regimen. The addition of a rapid-acting insulin (such as insulin lispro) 0.25 U/kg prior to the evening meal (Figure 4B) resulted in the eAG and HbA1c lowered to 144 mg/dL and 6.6%, respectively. Administering 0.2 U/kg insulin lispro prior to the morning and midday meals and 0.25 U/kg prior to the evening meal, along with bedtime insulin glargine (Figure 4C), resulted in eAG and HbA1c lowered to 128 mg/dL and 6.1%, respectively. The simulations of premixed formulations of intermediate-acting and rapid-acting insulins (75% ILPS and 25% insulin lispro [Mix 75/25]) at a dose of 0.3 to 0.4 U/kg administered twice a day prior to morning and evening meals showed blood glucose was controlled throughout the day and night (Figure 4D) and had an eAG of 131 mg/dL and an HbA1c of 6.2%. The simulation of 50% ILPS and 50% insulin lispro (Mix 50/50) at a dose of 0.2 to 0.35 U/kg administered 3 times a day, prior to morning, midday, and evening meals (Figure 4D), achieved comparable blood glucose concentrations to Mix 75/25 twice daily and had an eAG of 137 mg/dL and an HbA1c of 6.4%.

Example 2. Daily lifestyle choices can affect the insulin therapy needs of patients with T2DM, so the insulin regimen may need to be adjusted to best suit the patient. During the month of Ramadan, Muslims who fast must abstain from eating and drinking from predawn to after sunset. Hence, patients with diabetes would also alter their eating patterns to 2 meals a day at predawn and after sunset, thus skipping the lunch meal. Because of their chronic metabolic disorder, coupled with a change in dietary habit and timing of meals, insulin regimens for patients with diabetes must be adjusted accordingly during Ramadan to maintain glycemic control and minimize the risk of
Figure 5. Simulated blood glucose over time for patients with T2DM given (A) premixed insulin lispro (Mix 75/25) at mealtimes versus insulin profiles following different scenarios of dosing regimen adjustments during the month of Ramadan such as (B) skipping lunch dose with lower premixed insulin dose at breakfast followed by the usual premixed dose at dinner; (C) skipping lunch dose with slightly lower dose at breakfast and at dinner; and (D) skipping lunch dose with slightly lower dose at breakfast and a premixed formulation with higher lispro ratio (Mix 50/50) at dinner time to address the heavier evening meal. The shaded area represents the time interval during which a patient is fasting. The dashed line represents the average daily glucose. The mealtime and carbohydrate amount in the meals are indicated on the x axis. The hypothetical patient conditions assumed for the simulation include body weight of 80 kg and caloric intake of 30 kcal/kg/day with 50%–60% of calories derived from carbohydrates prior to Ramadan and a 50%–70% reduced carbohydrate consumption during Ramadan observance. A, AM; MN, midnight; Mix 75/25, premixed 75% insulin lispro protamine suspension and 25% insulin lispro; Mix 50/50, premixed 50% insulin lispro protamine suspension and 50% insulin lispro; P, PM.

Example 3. Adherence to rapid-acting insulin dosing at mealtimes may be challenging because of varying eating habits and lifestyle. The linked subcutaneous insulin PK and IGI model was used to explore the blood glucose response following the subcutaneous administration of a rapid-acting insulin prior to or after a meal. In this example, a hypothetical 85-kg patient with T2DM with a mealtime bolus dose of insulin lispro 20 U and a target postprandial glucose of 140 mg/dL was simulated. The administration time of insulin was varied between 30 minutes prior to and after the start of the meal (Figure 6A). In addition, the amount of carbohydrates in the meal was decreased from 120 g down to 15 g. The postprandial peak glucose is lower when insulin lispro is administered prior to the meal start compared with insulin lispro injected after the meal (Figure 6B). The simulation indicates that if only 50% of the usual total carbohydrates was eaten, injecting insulin lispro up to 30 minutes after the start of the meal was associated with postprandial peak glucose close to the target of 140 mg/dL (Figure 6C). When less than 50% of the usual total carbohydrates was eaten, a decrease or omission of the insulin dose should be considered, as blood glucose decreased below baseline when the full insulin dose was administered.
Figure 6. Simulated insulin lispro over time following administration of insulin lispro 20 U at times prior to and after meal start (A) and the associated blood glucose over time for patients with T2DM with meal carbohydrate amounts of 120 g (B), 60 g (C), or 15 g (D). The solid line represents insulin lispro or glucose with insulin treatment. The dashed line represents the glucose without insulin lispro administration. The mealtime and carbohydrate amount in the meals are indicated on the x axis. The hypothetical patient conditions assumed for the simulation include body weight of 85 kg.

(Figure 6D). The results of the simulation may be useful illustrations supporting potential advice from health care practitioners to patients with T2DM with fluctuating eating patterns.

Discussion
The PK of insulin was consistent across populations of healthy volunteers, patients with T1DM, and patients with T2DM, after accounting for patient factors such as body weight. Simulated insulin concentration-over-time curves based on PK parameters estimated from data from healthy volunteers were consistent with observed data from patients with T1DM or T2DM. Population PK analysis of insulin concentrations following administration of regular insulin, insulin lispro, or a mixture of insulin lispro and ILPS yielded parameter estimates comparable to previously published values for healthy volunteers, confirming the robustness of the model-predicted PK parameters. The similarity
of exogenous insulin disposition between healthy volunteers and patients with T1DM or T2DM permits pooling of data from multiple clinical studies to support robust characterization of subcutaneous insulin PK. A comprehensive characterization of insulin disposition following subcutaneous insulin administration allows for a better understanding of the impact of the insulin concentration-time course on glucose response.

The IGI model has been extensively developed with data from healthy volunteers and patients with T2DM, and the differences between populations in some IGI model parameters, such as baseline glucose, baseline insulin, and insulin-dependent clearance of glucose, have been previously discussed. With some modifications to the IGI model structure and parameter values, profiles of insulin and glucose concentrations over time, consistent with observed data from patients with T1DM or T2DM, were generated. The fractional scalar parameter to adjust the subcutaneous insulin effect on the clearance of glucose relative to endogenous insulin is likely related to the difference between the total amount of insulin secreted by the pancreas and the plasma measurement of insulin after insulin is removed by the liver. The hepatic extraction of insulin has been estimated to be 62% based on insulin and C-peptide data collected from healthy volunteers who participated in a 24-hour euglycemic clamp study without insulin injection. The absorption of glucose derived from meals was explored using either a single first-order rate constant or a more structurally complex transit compartment approach that is representative of the gastrointestinal tract. The mechanism-based approach permitted greater flexibility in the IGI model to capture the rise of glucose following an assortment of meals with varying nutrient compositions.

Linking the subcutaneous insulin PK model to the IGI model was a valuable method to explore and visualize profiles of insulin and glucose concentrations over time after incorporating the impact of hypothetical real-world input, such as patient baseline conditions and demographics, insulin formulation, insulin dose amount, and carbohydrate amount. To further improve the predictive ability of the IGI model, additional model development may be needed. Applying the linked subcutaneous insulin PK-IGI model to glucose data from more clinical studies would enable robust estimation of the endogenous glucose and insulin parameters and their associated between-subject variability to improve the understanding of potential differences between healthy subjects and patients with T1DM or T2DM. Although insulin-glucose models can be used for individualized insulin dosing, as demonstrated by the research conducted for artificial pancreas systems with continuous subcutaneous insulin infusion pump therapy in patients with T1DM, the application of the IGI model is better suited for evaluating dosing decisions that affect the diabetic population. The prospective use of IGI model-based simulation to evaluate the impact of various rapid-acting mealtime insulin dose-titration algorithms on glycemic control in patients inadequately controlled on basal insulin glargine and metformin has been published. The IGI model-based simulations were used to identify optimal titration algorithms that were subsequently evaluated in a clinical trial.

The linked subcutaneous insulin PK-IGI model could possibly be expanded to improve the characterization and understanding of current and future diabetes treatment options on glucodynamics. The efficacy of drugs given in combination with insulin could be investigated by including the effect of non-insulin hormones (eg, glucagon, glucose-dependent insulino tropic polypeptide, and glucagon-like peptide 1) into the IGI model. Incorporating nonpharmacological influences on glucose homeostasis, such as the diurnal pattern of metabolism, the impact of body weight changes, the effect of noncarbohydrate nutrients (eg, fats and protein), and the absorption of complex carbohydrates may enrich the predictive capability of the IGI model for real-world conditions and could possibly help to provide improved guidance for the safe and efficacious use of insulin treatment.

The utility of PK-PD models for assessing drug efficacy in diabetes drug development has been demonstrated repeatedly over the past decade. The linked subcutaneous insulin PK-IGI model has application to currently available formulations and may be useful in the development of future insulin treatments by providing a framework to explore the impact of modified insulin PK on glucodynamics and enabling simulations that allow for assessment of potential safety and efficacy. With the availability of software, such as the R web browser toolkit package, Shiny, visualization of predictions from complex models of glucose homeostasis can be more readily accessible by and shared with clinicians. The linked subcutaneous insulin PK-IGI model is a valuable tool to facilitate research of diabetes therapy and could potentially be used to support clinical education on insulin treatment and pharmacology.

Conclusions

Complex models describing insulin and glucose concentrations over time in patients with T1DM or T2DM can be implemented and utilized as a means to ease and enhance comprehension of the impact of insulin treatments on glucose profiles. Coupled visualizations of insulin and glucose response to various insulin formulations and patient factors may help health care
practitioners better understand how insulin regimens may meet the needs of patients over a wide range of simulated scenarios.

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 Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.