Human insulin dynamics in women: a physiologically-based model

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ABSTRACT
Currently available models of insulin dynamics are mostly based on the classical compartmental structure and thus their physiological utility is limited. In this work, we describe the development of a physiological-based model and its application to data from 154 patients who underwent an insulin-modified intravenous glucose tolerance test (IM-IVGTT). In order to determine the time profile of endogenous insulin delivery without using C-peptide data and to evaluate the transcapillary transport of insulin, the hepatosplanchnic, renal and peripheral beds were incorporated into the circulatory model as separate subsystems. Physiologically reasonable population mean estimates were obtained for all estimated model parameters, including plasma volume, interstitial volume of the peripheral circulation (mainly skeletal muscle), uptake clearance into the interstitial space, hepatic and renal clearance, as well as total insulin delivery into plasma. The results indicate that, at a population level, the proposed physiological-based model provides a useful description of insulin disposition, which allows for the assessment of muscle insulin uptake.

Keywords
Insulin transport; intravenous glucose test; insulin delivery; circulatory model; population analysis
INTRODUCTION

Insulin administration continues to be an important therapy in treating patients with type 1 and also type 2 diabetes mellitus. Some newer classes of pharmacotherapies, moreover, act by stimulating endogenous insulin secretion, including incretin analogues and DPP-4 inhibitors (20). Thus a more complete understanding of the pathophysiology of insulin dynamics may lead to improved management of diabetes in patients treated with insulin or with therapies that promote endogenous insulin release.

Insulin disposition in humans has been studied previously using compartmental analysis to quantify the kinetic of insulin’s distribution and elimination (see (6) for a review). While such compartment models for insulin dynamics are useful for describing plasma insulin concentration-time profiles (e.g., following intravenous, subcutaneous and inhaled insulin administration), a drawback of the reported one (15), two (23) and three (27) compartment mammillary models, including time varying (21) and nonlinear models (16), is that the model compartments have little anatomical and physiological correspondence. As a consequence the model and its parameters cannot be readily interpreted in terms of fundamental transport mechanisms that underlie the distribution and elimination of insulin. For example, previously reported compartment models do not provide information on the dynamics of insulin uptake by skeletal muscle tissue, yet such information is valuable since muscle uptake of insulin is the rate-limiting step in insulin stimulated muscle glucose uptake (1, 3). Moreover, the mechanism of this transport process remains unclear (2, 18). These compartment models, furthermore, do not readily allow for prediction of insulin dynamics in patient populations with liver, cardiovascular,
kidney and other relevant diseases, and as such provide limited ability to reflect changes in insulin disposition in disease progression.

To address the aforementioned limitations of current models of insulin dynamics, we have developed a physiologically-based pharmacokinetic (PBPK) model for insulin disposition using plasma glucose and insulin time course data from patients who underwent a frequently sampled insulin modified-intravenous glucose tolerance test (IM-IVGTT) to determine beta-cell function and insulin sensitivity (11, 29, 32, 37). The specific aims of the study were to use the insulin concentration data from the IM-IVGTT test obtained in healthy females and in women at risk for developing diabetes to construct a physiological-based circulatory model of insulin dynamics in humans as a tool which will allow the evaluation of the uptake of insulin into the skeletal muscle, and the estimation of both hepatic and renal clearance of insulin.

MATERIALS AND METHODS

Participants and Study Design. Women who previously exhibited gestational diabetes (that is, who are at risk for developing diabetes) and women who had normal pregnancies were recruited from the outpatient department of the University Clinic of Vienna. The details of the clinical study, including the ethical committee’s approvals, have been reported elsewhere (37). A total of 120 who previously exhibited gestational diabetes and 34 women who had normal pregnancy had complete data and were used in the analysis reported herein. The anthropometric characteristics of these 154 women are as follows:
body weight: 73± 16 kg; body mass index: 27± 6 kg/m²; age: 33± 5 - mean ± standard deviation). All women underwent IM-IVGTT 8 to 10 weeks postpartum. After a 10- to 12-hour overnight fast, bolus doses of glucose (0.3 g/kg) and insulin (0.3 U/kg in 1 min) were given at time 0 and 20 min, respectively. Insulin was measured in samples taken immediately before glucose ingestion and at 0, 3, 4, 5, 6, 8, 10, 14, 19, 22, 27, 30, 35, 40, 50, 70, 100, 140, and 180 min after glucose injection. Blood was rapidly centrifuged and insulin was determined in plasma by commercially available radioimmunoassay (Serono Diagnostics, Freiburg, FRG) providing an inter-assay coefficient of variation of 5%.

Model. The structure of the PBPK model used in this study is depicted in Fig. 1. It represents the simplest possible model for analyzing the following processes governing insulin’s dynamics: uptake into the interstitial space, pancreatic secretion, hepatic extraction and renal elimination. The model consists of subsystems representing the pulmonary (distribution volume $V_P$) and systemic circulation, with the latter separated into the splanchnic circulation, the kidneys ($V_K$) and the rest of the systemic circulation as three parallel subsystems. The splanchnic circulation is formed by the liver ($V_L$), together with the gastrointestinal tract including spleen and pancreas ($V_G$) arranged in series. In the peripheral circulation (mainly skeletal muscle), permeation through the capillary wall, from the plasma compartment ($V_1$) to the interstitial space ($V_2$) is determined by the permeability-surface product ($PS$). Cardiac plasma output is denoted by $Q$. The parameters $q_L$ and $q_K$ indicate the fractions of blood flow to the liver and kidney, while $q_{Ha}$ and $q_{Pv}$ represent hepatic artery and portal vein blood flow (all parameters defined in Table 1). The posthepatic delivery rate of insulin, $I(t)$, consists of a constant basal rate,
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\( I_{basal} \), and the response due to glucose injection. For the time course of the latter, a specific pattern has been assumed \textit{a priori} as depicted in Fig. 1. It is a simplified form of \( I(t) \) profiles reported in the literature (10, 19) and consists of a supra basal phase 1 (peak) rate lasting 3.5 min (\( I_{phase1} \)) followed by a reduced phase 2 rate lasting 17 min (\( I_{phase1}/6 \)). Based on a well-mixed organ model, the intrinsic clearances \( CL_{int,L} \) and \( CL_{int,K} \) account for hepatic extraction (metabolism) and renal elimination of insulin. The complete set of equations describing the model shown in Fig. 1 is provided in the Appendix. Since all patients were in a fasted state when the IM-IVGTT was initiated, the model was assumed to be in steady state prior to glucose administration (see Appendix for further details).

In order to select the most parsimonious model of insulin distribution in the peripheral circulation, the two-compartment tissue model was compared to both simpler and more complex models. The alternate models included a one-compartment (flow limited) distribution model, and a model with a saturable (Michaelis-Menten) uptake process and lymphatic back-transport from the interstitial space to the venous pool. We have neglected extraction since it was not possible to estimate separately insulin clearance by the kidney and the rest of the peripheral circulation. Non-blood flow limited models for the other organs and tissues were not supported by the experimental data of the IM-IVGTT study used in the current work.

Parameter Estimation and Statistical Analysis. The insulin concentration-time data from all patients were analyzed simultaneously using a hierarchical, population modeling approach that allows information from the separate patients to collectively inform the model estimation. The hierarchical modeling analysis yields estimates of the population
mean and inter-patient variability for those estimated parameters of the tested models, as well as their precision as percent relative standard error (%RSE). Furthermore, estimates of the individual subject parameters are available. The hierarchical analysis was accomplished via maximum likelihood estimation using the expectation-maximization algorithm (MLEM) in the ADAPT (version 5) software for pharmacokinetic/pharmacodynamic system analysis (8). Estimated model parameters were assumed to follow a multivariate log-normal distribution and the error associated with measured insulin was assumed to be normally distributed with standard deviation dependent on insulin (additive and proportional error terms). Model selection for insulin distribution was based on the resulting values of the Akaike Information Criterion (AIC) for the tested models (as implemented in (8)), as well as on the plausibility of estimated model parameters.

The model parameters $V_1$, $V_2$, $PS$, $CL_{int,L}$, and $CL_{int,K}$ as well as $I_{basal}$ and $I_{phase1}$ were estimated using the data, while the parameters $VP$, $VG$, $VL$, $VK$, $VP$, were determined based on $V_1$ and $Q$, $q_K$, $q_{Ha}$ and $q_{Pv}$ were fixed (Table 1). Volumes were estimated as fraction of body weight ($BW$) and cardiac plasma output as a power function of $BW$.

Other relevant quantities were derived from the estimated and fixed model parameters. For the one compartment liver model (see Fig. 1), the hepatic clearance was obtained as follows ($q_L=q_{Ha}+q_{Pv}$)

$$CL_{hep} = \frac{q_L Q CL_{un,L}}{q_L Q + CL_{un,L}}$$  
(1)
An analogous formula (one compartment organ model) was used to calculate renal clearance, $CL_{\text{ren}}$, and thus the total clearance of insulin is given by the sum $CL_{\text{hep}} + CL_{\text{ren}}$.

From Eq. 1 the hepatic extraction ratio ($E_{\text{hep}}$) of insulin was obtained as

$$E_{\text{hep}} = \frac{CL_{\text{int,I}}}{q_L Q + CL_{\text{int,I}}}$$ (2)

The total insulin delivery ($TID$), i.e. the total amount of insulin delivered after hepatic degradation, was calculated from the estimated delivery rate of insulin above basal as follows:

$$TID = \int_0^{20.5} I(t)dt - \int_0^{20.5} I_{\text{phase}_1}dt$$ (3)

Based on Eqs. (2) and (3) and the total insulin secretion ($TIS$) was calculated as:

$$TIS = TID / \left(1 - E_{\text{hep}}\right)$$ (4)

Multiple comparison inference was performed using the non-parametric Kruskal-Wallis test.

RESULTS

Figure 2 shows insulin plasma concentration (mean and standard deviation) for all patients from each group. The mean insulin concentration time curves for the women who previously exhibited gestational diabetes and control groups were largely superimposable. Moreover, separate modeling analyses based on data from each group resulted in no significance differences in estimated model parameters (results not shown).
Thus the data from both groups were combined in the final model development and subsequent analysis presented below. The insulin concentration time profile predicted based on each patient’s model parameters (conditional mean estimates, derived and fixed) were averaged and are shown in Fig. 3 together with the mean and standard deviation of the measured insulin. The inset in Fig. 3 more clearly shows the ability of the population model to also describe the dynamics of insulin following glucose administration and prior to insulin injections. A composite graph showing a plot of the measured plasma insulin concentrations in all 154 patients versus the corresponding patient model predictions (2,926 values in total) demonstrates the goodness-of-fit obtained with the model (Fig. 4). Although some model over prediction is noted, the coefficient of determination for the regression line is $r^2 = 0.83 \ (P < 0.0001)$, indicating that the model fits the data with good fidelity over this wide range of plasma insulin values. Replacing the two-compartment tissue model by a one-compartment model (instantaneous distribution of insulin into the interstitial space) led to an increase in AIC (23,946 versus 23,493). No decrease in AIC was achieved by incorporating either a saturable uptake or lymphatic back-transport process into the model.

Table 2 lists the estimated population mean estimates for $V_1$, $V_2$, $PS$, $CL_{int,L}$, $CL_{int,K}$, $I_{basal}$ and $I_{phase1}$, together with their inter subject variability, obtained using the model shown in Fig. 1 (percent relative standard errors, %RSE, shown for each estimate). The table also shows the resulting values of the derived quantities including the hepatic clearance ($CL_{hep}$), renal clearance ($CL_{ren}$), hepatic extraction ratio ($E_{hep} \ (%)$), total insulin delivery ($TI$) and total insulin secretion ($TIS$), calculated based on the definitions
presented in the Materials and Methods section. The renal extraction ratio of 0.22 was for a BW = 70 kg, as determined using the value of renal flow in Table 1 and renal clearance in Table 2. As an example, Fig. 5 shows observed insulin concentrations together with model predictions (based on individual parameter estimates) for four selected patients with different insulin delivery rates. The subjects in panels a and b of Fig. 5 had lower values of total insulin delivery (0.26U and 0.27U) relatively to the mean population estimate (0.40U). The subject in the panel c had a TID (0.89U) closer to the population mean, while the subject in panel d had a considerably larger TID of 2.0U. Despite this greater than seven-fold difference in TID between these subjects, insulin dispositions as assessed by the total clearance varied over less than a two-fold range (303 ml/min for the subject in panel c to 477 ml/min for the subject in panel d).

DISCUSSION

To our knowledge, this is the first physiological-based circulatory model of insulin dynamics developed to describe insulin disposition following IM-IVGTT in humans. In addition to the exogenous insulin infusion from the IM-IVGTT protocol, the model accounts for the resulting endogenous post hepatic secretion of insulin (i.e., the basal level and the response to glucose stimulation), and divides the systemic system into three lumped subsystems: hepato-splanchnic, renal and remainder (largely skeletal muscle). The latter was modeled by a vascular space compartment and an interstitial space compartment with permeation controlled by the permeability surface area parameter (PS), which assumes that insulin uptake is mainly determined by skeletal
muscle. The model allows for estimation of hepatic insulin clearance and extraction, and an estimate of renal insulin clearance through the kidney subsystem included in the model.

The IM-IVGTT study upon which the current modeling analysis is based was designed for evaluating insulin sensitivity and not explicitly for the goal of modeling insulin disposition. However, by using prior information for certain model parameters (Table 1), exploiting the information in the measured insulin data from both the glucose and insulin administration portions of the IM-IVGTT protocol, and using a population modeling approach guided by prior information about liver and renal insulin clearance, reliable values were obtained for the estimated model parameters. Following the glucose dose of the IM-IVGTT protocol, the plasma insulin measurements provide information about the endogenous insulin secretion despite the simplified form of the pancreatic insulin release profile assumed. The large insulin dose given at 20 min provides considerable information about the phases of insulin disposition, especially muscle distribution parameters in the earlier phases of the disposition profile, along with total clearance from the later disposition phase. To investigate the reliability of the estimated skeletal muscle distribution parameters of the model (both population mean and intersubject variability), the population analysis was also performed with intrinsic insulin renal clearance fixed at 171 ml/min (the estimated value shown in Table 2) and at 243 ml/min (corresponding to a total renal clearance of 200ml/min). The resulting estimates for the skeletal muscle distribution parameters of the model (both population mean and intersubject variability) were largely unchanged regardless of the value used for the fixed
intrinsic renal clearance, providing some support for the reliability of the skeletal muscle distribution model.

Insulin Clearance and Hepatic Extraction. Hepatic extraction of insulin is an important contributor to its peripheral concentration, given that the liver filters approximately 50% (5, 6) of the secreted hormone before it reaches the systemic circulation. This process, however, is often ignored in metabolic studies involving the evaluation of insulin secretion and delivery to the periphery circulation, where it acts on glucose uptake. By using the model introduced here, it is possible to reflect the hepatic handling of insulin and quantify its contribution to the available systemic insulin concentration. The population estimates obtained from the population analysis of our circulatory model have been assessed by comparing them with directly measured quantities. The model-based estimates of hepatic and renal clearance were 363 and 141 ml/min, respectively, similar to the corresponding values of 320-400 and 200 ml/min reported in humans (14, 33). This holds also for the ratio of hepatic to peripheral clearance (28), assuming that renal extraction is the main contribution to the latter. The estimated mean hepatic extraction ratio of 46% is in accordance with values reported previously for humans (5, 6). The estimated total clearance, $CL_{hep} + CL_{ren}$, of 504 ml/min is somewhat lower than that of 716 ml/min reported in a pharmacokinetic study (23), which could be attributed to different subject populations and experiment designs. Note that the estimated parameter $CL_{int,L}$ is independent of blood flow; $CL_{hep}$ is a derived parameter that is dependent on hepatic blood flow (Eq. 1).
Muscle Distribution. The estimate of insulin distribution volume $V_1$ of 19.1 ml/kg is higher than the typical value of muscle blood volume reported for humans 12 ml/kg (17), but this is not unexpected in that $V_1$ in the model includes not only skeletal muscle blood volume but also that of other tissues of distribution. The $V_2$ estimate of 24.9 ml/kg obtained in the modelling analysis is smaller than the muscle interstitial volume of 39 ml/kg reported in (4), and may be due to the endogenous insulin level leading to a less well defined terminal insulin disposition phase. For the transendothelial insulin transport into the interstitial space a permeability-surface product (or uptake clearance) of 75.8 ml/min was estimated ($PS$ in the model), compared to a value of 105 ml/min measured directly in human skeletal muscle using microdialysis (13). A different model was used by Pretty et al. (24) to calculate uptake rate constants from arterial and interstitial insulin concentration data taken from various sources in the literature. Our results are also within the range of $PS$ values (11 and 91 ml/min) reported in (24). Our results do not suggest a saturable uptake of insulin, which is in agreement with some findings (3, 26), but not with others (16). Finally, the modeling results do not include the lymphatic back transport pathway, but this may be a consequence of the relatively short time course of this IM-IVGTT protocol during which any contribution of lymphatic transport to plasma insulin would be minimal.

Pancreatic Secretion and Systemic Delivery. Even though a simplified piece-wise constant shape of insulin delivery rate assumed in the present work, the resulting estimates of the underlying biphasic insulin secretion rates were within the range of values reported previously for the same dose of glucose (0.3 g/kg) in humans. The model
estimate of the maximum rate of insulin delivery ($I_{phase1}$, first peak in Fig. 1) was 61.2 mU/min, which is within the wide range of 43 to 181 mU/min reported in (10), but higher than that of 12 mU/min estimated by (31). The estimated basal delivery rate ($I_{basal}$ in Fig. 1) was 2.98 mU/min, which is lower than 7 mU/min reported in (22) and somewhat higher than the value of 0.95 mU/min reported in (31). Note that the calculation of insulin secretion (Eq. 4) is based on the assumption that insulin clearance is not saturated, as required by Eq. 2.

The objective of the work reported herein was to develop a PBPK model of insulin kinetics. To achieve this aim, given the clinical study design, it was necessary to assume both a time-constant hepatic extraction and a piece-wise constant pattern of insulin delivery as has been used previously (e.g., (34)). The simplified model used for insulin release, while appropriate for the patient population under study, would not be applicable more broadly as part of a complete IM-IVGTT model for other populations or study designs. Despite these limitations, the resulting overall PBPK model includes parameters representing the physiological properties that determine insulin disposition. We note that other model-based approaches such as those based on an empirical description of insulin disposition and C-peptide data allow the estimation of the time-dependence of extraction and the pattern of insulin secretion (30, 31). Insulin release profiles so obtained, could then be incorporated into the PBPK model for insulin disposition reported in this work.

In conclusion, the physiological-based model of insulin dynamics presented describes the IM-IVGTT insulin data obtained in this population of patients with reasonable fidelity.
As a consequence of the model’s physiological basis, it can be used to predict alterations in insulin dynamics that might be expected in diabetic complications involving cardiovascular system, as well as the liver and kidneys. Thus the model provides a framework for incorporating disease progression into predictions of insulin dynamics that may further inform insulin-based treatment of diabetes. Moreover, independent estimates of the model’s physiological parameters in individual subjects (e.g., noninvasive estimates of cardiac output) can be used to improve the model’s subject-specific predictive ability.

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GRANTS

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DISCLOSURES

The authors declare no conflicts relating to this study.


APPENDIX

The following equations define the circulatory model shown in Fig.1. The symbol $A_i$ is
the insulin amount in compartment $i$, $IV(t)$ is the insulin infusion rate and $C(t)$ denotes
the measured concentration. The definitions of the other symbols are provided in the text.
As described in Methods and Materials, they have been implemented in the ADAPT
software (8). Model assumptions are provided in the Materials and Methods section and
these include: simplified, two-phase form of $I(t)$; non-flow limited distribution in skeletal
muscle; flow limited update in all other organs/tissues; first-order liver and renal
clearances.

\[
\frac{dA_p}{dt} = IV(t) + I(t) + q_L Q \frac{A_L}{V_L} + q_K Q \frac{A_K}{V_K} + (1 - q_L - q_K) Q \frac{A_1}{V_1} - Q \frac{A_p}{V_p}, \quad A_p(0) = 0
\]
\[
\frac{dA_G}{dt} = q_p Q \left( \frac{A_p}{V_p} - \frac{A_G}{V_G} \right), \quad A_G(0) = 0
\]
\[
\frac{dA_L}{dt} = q_ho \frac{A_p}{V_p} + q_p Q \frac{A_G}{V_G} - q_L Q \frac{A_L}{V_L} - Cl_{int,L} \frac{A_L}{V_L}, \quad A_L(0) = 0
\]
\[
\frac{dA_K}{dt} = q_K \left( \frac{A_p}{V_p} - \frac{A_K}{V_K} \right) - Cl_{int,K} \frac{A_K}{V_K}, \quad A_K(0) = 0
\]
\[
\frac{dA_1}{dt} = (1 - q_L - q_K) Q \left( \frac{A_p}{V_p} - \frac{A_1}{V_1} \right) + PS \left( \frac{A_2}{V_2} - \frac{A_1}{V_1} \right), \quad A_1(0) = 0
\]
\[
\frac{dA_2}{dt} = PS \left( \frac{A_1}{V_1} - \frac{A_2}{V_2} \right), \quad A_2(0) = 0
\]
\[C(t) = \frac{A_1}{V_1}\]

The form of $IV(t)$ in the first equation above is depicted in Fig.1. A run-in period is
incorporated in $IV(t)$ for simulations to allow the estimated basal delivery rate ($Ib$) to
produce the corresponding non-zero basal values of insulin in all tissues prior to the start of the IM-IVGTT protocol (t=0 in Fig. 1).
Table 1. Parameters used in the model

<table>
<thead>
<tr>
<th>Estimated parameters</th>
<th>Estimated parameters</th>
<th>Estimated parameters</th>
<th>Estimated parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle plasma volume</td>
<td>$V_1$ (ml/kg)</td>
<td>Muscle interstitial volume</td>
<td>$V_2$ (ml/kg)</td>
</tr>
<tr>
<td>Permeability-surface product</td>
<td>$PS$ (ml/min)</td>
<td>Intrinsic hepatic clearance</td>
<td>$CL_{int,L}$ (ml/min)</td>
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<tr>
<td>Intrinsic renal clearance</td>
<td>$CL_{int,K}$ (ml/min)</td>
<td>Basal delivery rate</td>
<td>$I_{basal}$ (mU/min)</td>
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<tr>
<td>Derived parameters</td>
<td>Derived parameters</td>
<td>Derived parameters</td>
<td>Derived parameters</td>
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<tr>
<td>Hepatic clearance</td>
<td>$CL_{hep}$ (ml/min)</td>
<td>Renal clearance</td>
<td>$CL_{ren}$ (ml/min)</td>
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<tr>
<td>Renal clearance</td>
<td>$E_{hep}$ (%)</td>
<td>Hepatic extraction</td>
<td>$TID$ (U)</td>
</tr>
<tr>
<td>Total insulin delivery</td>
<td>$TID$ (U)</td>
<td>Total insulin secretion</td>
<td>$TIS$ (U)</td>
</tr>
<tr>
<td>Parameters derived from fixed ratios</td>
<td>Parameters derived from fixed ratios</td>
<td>Parameters derived from fixed ratios</td>
<td>Parameters derived from fixed ratios</td>
</tr>
<tr>
<td>Lung plasma volume</td>
<td>$V_P$</td>
<td>$V_1*1.1$</td>
<td>Ref. 35</td>
</tr>
<tr>
<td>Gut plasma volume</td>
<td>$V_G$</td>
<td>$V_1*0.34$</td>
<td>Refs. 17, 12</td>
</tr>
<tr>
<td>Liver plasma volume</td>
<td>$V_L$</td>
<td>$V_1*0.17$</td>
<td>Refs. 17, 12</td>
</tr>
<tr>
<td>Kidney plasma volume</td>
<td>$V_K$</td>
<td>$V_1*0.05$</td>
<td>Refs. 17, 25</td>
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<tr>
<td>Cardiac plasma output</td>
<td>$Q$</td>
<td>4000*(BW/70)^{0.71}</td>
<td>Ref. 7</td>
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<td>Flow fraction to hepatic artery</td>
<td>$q_{H,a}$</td>
<td>$Q*0.08$</td>
<td>Ref. 36</td>
</tr>
<tr>
<td>Flow fraction to portal vein</td>
<td>$q_{Pv}$</td>
<td>$Q*0.20$</td>
<td>Ref. 36</td>
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<tr>
<td>Flow fraction to kidney</td>
<td>$q_K$</td>
<td>$Q*0.17$</td>
<td>Ref. 36</td>
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Table 2. Population parameter estimates for the model of insulin distribution, elimination and secretion dynamics in patients undergoing an intravenous glucose tolerance test.

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Symbol</th>
<th>Mean (%)RSE</th>
<th>Interpatient CV % (%)RSE</th>
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<tbody>
<tr>
<td>Muscle blood volume&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$V_1$</td>
<td>19.1 (6)</td>
<td>49 (9)</td>
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<tr>
<td>Muscle interstitial volume&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$V_2$</td>
<td>24.9 (17)</td>
<td>81 (22)</td>
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<tr>
<td>Permeability-surface product</td>
<td>$PS$</td>
<td>75.8 (13)</td>
<td>64 (21)</td>
</tr>
<tr>
<td>Intrinsic hepatic clearance</td>
<td>$CL_{int,L}$</td>
<td>571 (22)</td>
<td>67 (27)</td>
</tr>
<tr>
<td>Intrinsic renal clearance</td>
<td>$CL_{int,K}$</td>
<td>171 (51)</td>
<td>65 (53)</td>
</tr>
<tr>
<td>Basal delivery rate</td>
<td>$I_{basal}$</td>
<td>2.93 (10)</td>
<td>80 (9)</td>
</tr>
<tr>
<td>Peak delivery rate</td>
<td>$I_{phase1}$</td>
<td>61.2 (8)</td>
<td>73 (10)</td>
</tr>
<tr>
<td>Hepatic clearance&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$CL_{hep}$</td>
<td>363</td>
<td>42</td>
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<tr>
<td>Renal clearance&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$CL_{ren}$</td>
<td>141</td>
<td>54</td>
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<tr>
<td>Hepatic extraction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$E_{hep}$</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Total insulin delivery&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$TID$</td>
<td>0.397</td>
<td>73</td>
</tr>
<tr>
<td>Total insulin secretion&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$TIS$</td>
<td>0.730</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> These volumes include muscle and all other tissues with the exception of the hepatosplanchnic organs and kidneys.

<sup>b</sup> The equations for these derived parameters are presented in Methods and Materials.
Fig. 1. Schematic structure of the circulatory model of insulin dynamics, with exogenous input (glucose (0.3 g/kg) as bolus dose at time 0 and insulin infusion (0.3 U/kg in 1 min) at time 20 min) and endogenous posthepatic delivery rate of insulin, $I(t)$. $C(t)$ denotes the sampled insulin concentration, Subsystems include the pulmonary and splanchnic circulation kidneys, and rest of the systemic circulation (mainly skeletal muscle). Model parameters are described in Table 1. (Bold letters denote those parameters estimated in the population analysis.) The posthepatic delivery rate of insulin, $I(t)$, is shown in the inset on the right. It is comprised of the basal delivery rate, $I_{basal}$, plus the assumed pattern of glucose-induced delivery consisting of a peak rate, $I_{phase1}$, followed by a reduced rate, $I_{phase1}/6$.

Fig. 2. Measured insulin plasma concentration data (mean±SD) for the 120 patients at risk for developing diabetes (open circles) and the 34 control subjects (open squares).

Fig. 3. Average of the 154 individual subject model predicted insulin concentration time curves, together with the measured plasma insulin values (mean±SD). The inset shows the same information from the time of glucose administration prior to insulin administration, with the ordinate shown on a linear scale.

Fig. 4. Goodness-of-fit plot showing the individual subject predicted vs. observed plasma insulin concentrations. The solid line represents the line of identity.
Fig. 5. Examples of individual predictions for four selected patients. The estimated total insulin delivery, $TID$ (U), for each patient is as follows: a) 0.26 U, b) 0.27 U, c) 0.89 U, d) 2.0 U.
\[ I(t) = (1-q_L-q_K)Q \]

\[ Q = \text{IV} \]

\[ V_P \]

\[ V_L \]

\[ V_G \]

\[ V_K \]

\[ C_{\text{int,L}} \]

\[ C_{\text{int,K}} \]

\[ q_{\text{Ha}} Q \]

\[ q_{\text{PV}} Q \]

\[ q_K Q \]

\[ C(t) \]

\[ PS \]

\[ V_1 \]

\[ V_2 \]

\[ I_{\text{basal}} \]

\[ I_{\text{phase1/6}} \]

\[ I_{\text{phase1}} \]

\[ 0 \quad 3.5 \quad 20.5 \quad \text{min} \]