## A Model for Glucose, Insulin, and Beta-Cell Dynamics in Subjects With Insulin Resistance and Patients With Type 2 Diabetes


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# A Model for Glucose, Insulin, and Beta-Cell Dynamics in Subjects With Insulin Resistance and Patients With Type 2 Diabetes

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*Type 2 diabetes mellitus (T2DM) is a progressive, metabolic disorder characterized by reduced insulin sensitivity and loss of beta-cell mass (BCM), resulting in hyperglycemia. Population pharmacokinetic-pharmacodynamic (PKPD) modeling is a valuable method to gain insight into disease and drug action. A semi-mechanistic PKPD model incorporating fasting plasma glucose (FPG), fasting insulin, insulin sensitivity, and BCM in patients at various disease stages was developed. Data from 3 clinical trials (phase II/III) with a peroxisome proliferator-activated receptor agonist, tesaglitazar, were used to develop the model. In this, a modeling framework proposed by Topp et al was expanded to incorporate the effects of treatment and impact of disease, as well as variability between subjects. The model accurately described FPG and fasting insulin data over time. The model included a strong relation between insulin clearance and insulin sensitivity, predicted 40% to 60% lower BCM in T2DM patients, and realistic improvements of BCM and insulin sensitivity with treatment. The treatment response on insulin sensitivity occurs within the first weeks, whereas the positive effects on BCM arise over several months. The semi-mechanistic PKPD model well described the heterogeneous populations, ranging from nondiabetic, insulin-resistant subjects to long-term treated T2DM patients. This model also allows incorporation of clinical-experimental studies and actual observations of BCM.*

***Keywords:*** *type-2 diabetes; insulin resistance; beta-cell function; NONMEM; peroxisome proliferator-activated receptor agonist*

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Type 2 diabetes mellitus (T2DM) is a progressive, metabolic disease characterized by reduced insulin sensitivity (S) and loss of beta-cell function, resulting in hyperglycemia. Fasting plasma glucose (FPG) and fraction-glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$) are used as biomarkers to assess short- and long-term glycemic control, respectively. In addition, measuring the endogenous fasting insulin level (FI) estimates of S and beta-cell function can be obtained.

Population pharmacokinetic-pharmacodynamic (PKPD) modeling[1] is a powerful method to characterize relationships between drug exposure and biomarkers in T2DM.[2-4] A mechanistic approach can provide better understanding of drug action and disease. In addition, data from different studies, including heterogeneous patient populations and experimental conditions, can be used, and such models will likely have better predictive power. One prediction of interest is the effects of antidiabetic therapies on long-term disease progression, based on data from relative short-term studies (eg, 1 year or less).

In recent years, several PKPD models have been developed for T2DM and the pharmacodynamics of oral antidiabetics.[5] A semi-mechanistic model developed by de Winter et al[4] included disease progression and the interplay between FI, FPG, and $HbA_{1c}$. This population PD model was based on 2 large phase III studies in drug-naive patients treated with

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pioglitazone, metformin, or gliclazide and incorporated components for beta-cell function and insulin sensitivity and further attempted to distinguish immediate treatment effects from effects on long-term disease progression. The population PKPD model developed by Hamrén et al[3] incorporated the characteristics of red blood cell (RBC) aging and glycosylation of Hb and was based on a phase II study investigating the effects of 12 weeks' treatment with tesaglitazar in both drug-naive subjects and patients previously on antidiabetic medication. As for other peroxisome proliferator-activated receptor (PPAR) agonists,[6] tesaglitazar has been observed to decrease Hb in a dose- and time-dependent manner,[7,8] which was incorporated in the model.

A semi-mechanistic model that integrates beta-cell mass (BCM), insulin, and glucose dynamics has been proposed by Topp et al.[9] To our knowledge, this model, derived from different sources in the literature, has never been applied to clinical data. Furthermore, Topp et al[9] remark that the model neither incorporates the effects of antidiabetic treatment nor all known physiological effects. In the present study, the underlying structure in the Topp model was used and further developed with data from 3 clinical studies (phase II/III) with tesaglitazar.

Tesaglitazar is a dual PPAR $\alpha/\gamma$ agonist previously in development for treatment of T2DM. Clinical development was discontinued in May 2006 when results from phase III studies indicated that the overall benefit-risk profile was unlikely to give patients an advantage over currently available therapies. Tesaglitazar activates PPAR $\alpha/\gamma$, which increases insulin sensitivity in liver, fat, and skeletal muscle cells; increases peripheral glucose uptake; and decreases hepatic glucose output, similar to the effects of PPAR$\gamma$ agonists such as rosiglitazone and pioglitazone.[10] When treatment with PPAR agonists is initiated, the response in FI is relatively rapid, and a pseudo steady state is reached within weeks after initiation of treatment. However, the decline in FPG is slower, with a pseudo steady state reached within months.[4] This pattern is probably a result of slowly increasing BCM[11-14] simultaneous to the enhanced insulin sensitivity that follows with improved lipid metabolism.[15] For accurate predictions of long-term disease-modifying effects, the treatment effects seen over the first 6 months have to be separated from the underlying disease progression and any protective effects that treatment may have on this process.

Our model predictions of BCM assume that beta-cell function per mg BCM is the same *during fasting* in T2DM patients and normal, healthy subjects. Consequently, our predicted BCM may be seen as functional rather than actual BCM. On the other hand, as seen later in this work, our predicted BCM is in accordance with reports from autopsy studies, giving some support to this model assumption. Also, it should be emphasized that our BCM is mechanistically closer to the actual BCM than the beta-cell function calculated through the homeostasis model assessment (HOMA)[16] used in the model by de Winter et al.[4] As a measure of BCM, the HOMA beta-cell function is confounded by the deteriorating insulin sensitivity and insulin clearance that occurs with progressing diabetes.[17-19] Indeed, HOMA does not intend to measure BCM and is instead useful as a measure of how much a subject's beta-cell function would have to increase to obtain normoglycemia, all other disease-related factors remaining the same.

The purpose of this work was to further develop the semi-mechanistic model suggested by Topp et al[9] to better describe the dynamics of FPG, FI, S, and BCM with and without antidiabetic treatment in a heterogeneous population, including insulin-resistant subjects and patients at different T2DM disease stages.

## METHODS

### Trial Design and Participants

Three completed clinical phase II/III trials with tesaglitazar were included in the analysis: the Study in Insulin Resistance (SIR, SH-SBT-0001), a dose-finding study in nondiabetic subjects with hypertriglyceridemia and abdominal obesity (ie, signs of insulin resistance)[7]; the Glucose and Lipid Assessment in Diabetes (GLAD, SH-SBD-0001) trial, a dose-finding study in T2DM patients[8]; and the phase III GALLANT6 (D6160C00030) trial, a 6-month study with 0.5 and 1 mg of tesaglitazar compared with 3 doses of pioglitazone.[20] Subjects in the pioglitazone arm were excluded from the current analysis. The GLAD and GALLANT6 studies included both drug-naive patients and patients treated with oral antidiabetic medication prior to the study. For brevity, these patients are referred to as naive and pretreated.

The total number of participants treated with tesaglitazar or placebo in the 3 studies was 1460. Available data were tesaglitazar plasma concentrations (C), FPG, FI, Hb, and, except for the SIR study, also $HbA_{1c}$ (see Table I).

### Semi-Mechanistic PKPD Model Including Fasting Insulin and Beta-Cell Mass

Topp et al[9] proposed a model for BCM (fasting) insulin and glucose dynamics in normal subjects. In the current

**Table I** Study Design and Patient Characteristics at Study Entry

| Study | Run-In Duration, d, Mean (Range) | Treatment duration, d, Mean (Range) | Number of Observations Per Subject, Mean (Range) | | | | Investigated Doses, mg | Pretreatment, DGR | Number of Subjects | FPG, mmol/L, Mean (SD) | FI, pmol/L, Mean (SD) | Hb, g/L, Mean (SD) | $HbA_{1c}$, %, Mean (SD) | Sex, % Male | Body Weight, kg, Mean (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | FPG | FI | Hb | $HbA_{1c}$ | | | | | | | | | |
| SIR | 55 (41-92) | 78 (10-101) | 8.6 (3-10) | 6.4 (2-8) | 6.5 (2-8) | 0 (0-0) | 0, 0.1, 0.25, 0.5, 1 | Naive(1) | 377 | 5.9 (0.7) | 94.9 (70.2) | 147 (11) | — | 77 | 94.5 (15.7) |
| GLAD | 43 (20-67) | 73 (1-107) | 9.8 (4-13) | 6.3 (2-8) | 7.6 (2-14) | 3.8 (1-6) | 0, 0.1, 0.5, 1, 2, 3 | Naive (2) | 130 | 9.0 (1.5) | 74.8 (52.1) | 147 (11) | 7.3 (1.4) | 63 | 91.8 (17.2) |
| | | | | | | | | Pretreated (4) | 282 | 8.5 (1.7) | 70.7 (48.5) | 146 (13) | 7.0 (1.1) | 57 | 87.6 (17.8) |
| GALLANT6 | 58 (42-105) | 152 (1-190) | 9.5 (4-10) | 1.9 (1-2) | 8.7 (2-10) | 9.4 (4-10) | 0.5 and 1 | Naive (3) | 81 | 9.4 (1.5) | 90.9 (56.5) | 147 (10) | 7.8 (0.6) | 48 | 92.0 (23.3) |
| | | | | | | | | Pretreated (5) | 590 | 7.5 (1.7) | 84.1 (60.4) | 145 (14) | 6.7 (0.9) | 53 | 90.1 (20.4) |

FPG, fasting plasma glucose; FI, fasting insulin; Hb, hemoglobin; $HbA_{1c}$, fraction-glycosylated hemoglobin $A_{1c}$; DGR, disease group; SIR, Study in Insulin Resistance; GLAD, Glucose and Lipid Assessment in Diabetes.

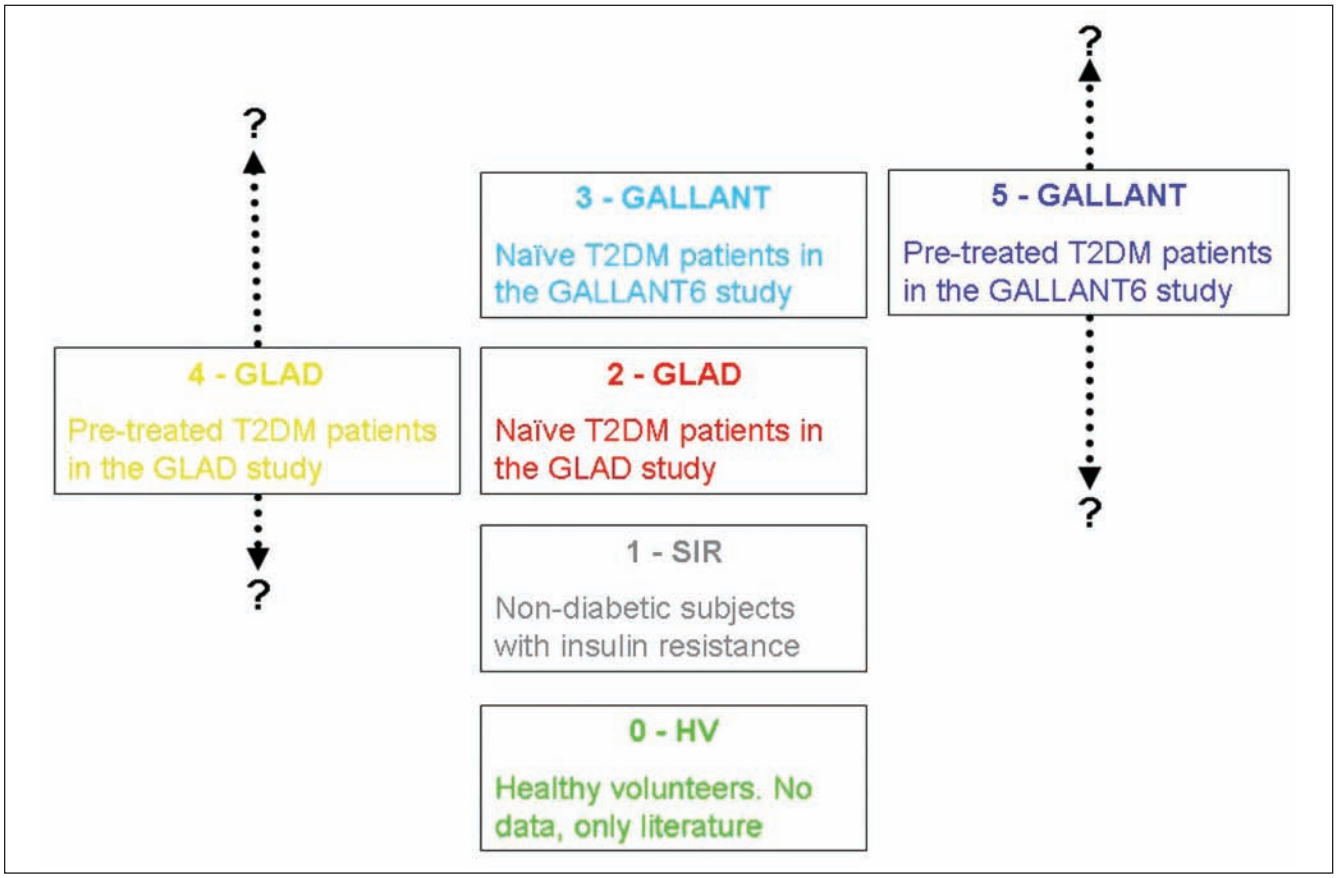


*Figure 1. Illustration of the disease stage in healthy volunteers and the 5 different disease groups (DGR). The typical drug-naive patients in the SIR, GLAD, and GALLANT6 studies can be assumed to have an increasing degree of diabetes. However, it is not obvious how to rank the pretreated patients in relation to the drug naive in the same study. (Figures online are in color.)*

investigation, their model structure was used as a starting point for further development. Treatment effects and impact of disease state on insulin sensitivity (S) and BCM[21] were added. Model parameters presented by Topp et al[9] represent mean values for healthy individuals. However, these values may change with T2DM. In the present data, 5 different disease groups (DGR) were defined as subjects with insulin resistance in SIR (DGR 1), naive patients in GLAD and GALLANT6 (DGR 2 and 3, respectively), and pretreated patients in GLAD and GALLANT6 (DGR 4 and 5, respectively). These disease groups could be assigned to different stages of disease,[21] as illustrated by Figure 1.

The net changes for FPG, FI, and BCM are described by 3 linked differential equations. These are summarized in the Online Appendix Part 1 (OA1) and motivated in the Topp et al[9] article. The new semi-mechanistic PKPD model was developed based on these equations. Progression into diabetes was described by a decreased S and a disturbed adaptation of the BCM. The insulin effect on lowering FPG is the product of S, FI, and FPG (equation 9 in OA1). Reduced insulin sensitivity alone does not cause diabetes because beta-cell adaptation acts as a negative feedback, eventually bringing the FPG back to the set point, as illustrated by Figure 2 (and further described by equation 11 in OA1). This phenomenon is found in insulin-resistant subjects, as studied in the SIR study. However, the feedback is not fully functional in T2DM patients where BCM is lower than in non–diabetic subjects.[22-25] The impact of disease stage on beta-cell adaptation was implemented as an offset in beta-cell adaptation (OFFSET) leading toward a higher set point FPG, thereby altering the equation for change in BCM to

$$dBCM_{it}/dt = (-d_0 + R_1 \cdot FPG'_{it} - R_2 \cdot FPG'^{2}_{it}) \cdot BCM_{it}, \quad (1)$$

$$FPG'_{it} = FPG_{it} - OFFSET_{it}, \quad (2)$$

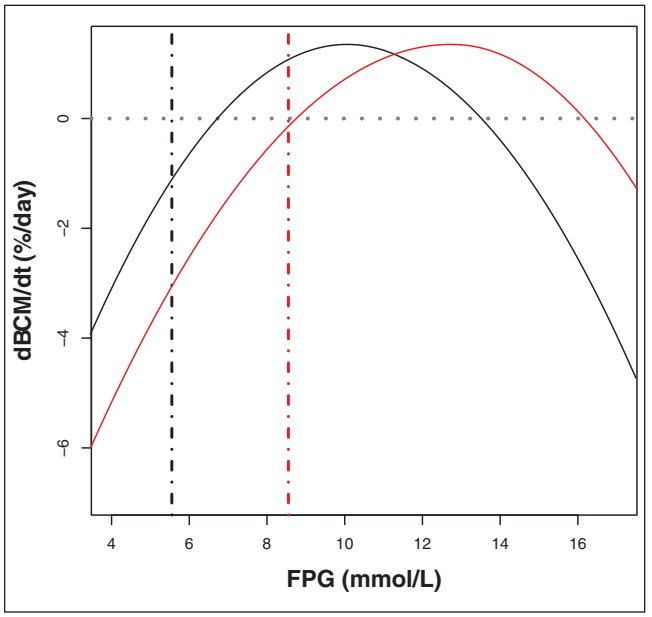


*Figure 2. Beta-cell adaptation rate versus fasting plasma glucose (FPG). The black curve represents the change in a healthy individual and the gray (online: red) in an offset (T2DM) patient. The dotted vertical lines mark the physiological fixed points in each of the 2 individuals. This is a point of attraction, and beta-cell adaptation acts with a negative feedback to bring the FPG back to this set point. At FPG much higher than the physiological fixed-point, severe glucose toxicity causes a positive feedback (below the horizontal line). However, such a serious condition, with accelerating loss of beta cell mass (BCM), would only be reached if the system was provoked (eg, by continuous glucose infusion).*

where $FPG'_{it}$ is the offset-corrected FPG for individual i at time t, and the other parameters are described in OA1, as well as in the original article by Topp et al.[9] In T2DM patients, $FPG_{it}$ is higher than $FPG'_{it}$ because the offset is causing a hyperglycemic FPG set point. The equation also includes glucose toxicity to the beta cells ($R_2$). Beta-cell adaptation at different FPG levels is illustrated for a healthy and an offset (ie, T2DM) individual in Figure 2.

The initial modeling attempts were not successful in describing treatment effects as observed: FI decreased faster than expected given the model parameters and the decline in FPG. Therefore, a relation between insulin clearance and insulin sensitivity[17-19] was incorporated into equation (10) according to

$$k_{it} = k_H \cdot (S_{it}/S_H)^{REL_{k-S}}, \quad (3)$$

where $S_{it}$ and $k_{it}$ are the insulin sensitivity and insulin elimination rate constant in individual i at time t, respectively. $S_H$ and $k_H$ are the values for the typical healthy subject. $REL_{k-S}$ describes the nonlinear relation between S and k.

Because study durations were 6 months or shorter, no attempt was made to quantify disease progression during the study period. In addition, because only *fasting* glucose and insulin were collected, it was assumed that these variables were at steady state with respect to each other, given the current level of BCM and $S_{it}$. Furthermore, at the first visit, it was assumed that subjects had obtained steady state in BCM and $S_{it}$. The mathematical implications of these assumptions are explained in OA1.

## Drug Effect and Statistical Submodels

Treatment effects were incorporated directly on OFFSET, where effect delay was accounted for by beta-cell adaptation, and on insulin sensitivity, where the effect was as implemented as an indirect response. FPG offset ($OFFSET_i$) and $S_i$ and were improved by treatment according to

$$FPG'_{it} = FPG_{it} - OFFSET_i \cdot (1 - E_{Bit}), \quad (4)$$

$$dS_{it}/dt = k_{in} \cdot (1 + E_{Sit}) - k_{out} \cdot S_{it}, \quad (5)$$

where $E_{Bit}$ is the treatment effect on the OFFSET for individual i at time t, $E_{Sit}$ is the indirect effect on insulin sensitivity, and $k_{out}$ is the rate constant determining the time course of the indirect response on S. Finally, $k_{in} = k_{out} \cdot S_i$, where $S_i$ represents the insulin sensitivity without treatment effect, that is, an underlying (baseline) *parameter*. The "observed" insulin sensitivity ($S_{it}$), on the other hand, is a *variable* that may change with treatment over time (t) and replaces S in the original equation (9) in OA1.

The effect of prior antidiabetic treatment at enrollment was incorporated on beta-cell adaptation ($pret_B$, which is $E_B$ at enrollment) and insulin sensitivity ($pret_S$, which is $E_S$ at enrollment). The interdependencies between tesaglitazar exposure, FPG, FI, S, and BCM in the model are schematically illustrated in Figure 3.

The model described differences in the degree of disease between DGR and even between individuals within the same DGR; the latter was achieved using a population model, in this case a nonlinear mixed effects model. All models were fitted using the population PKPD software NONMEM.[26] A population model takes into account that model parameter values vary between individuals, both due to known factors (eg, DGR) but also due to factors that are not

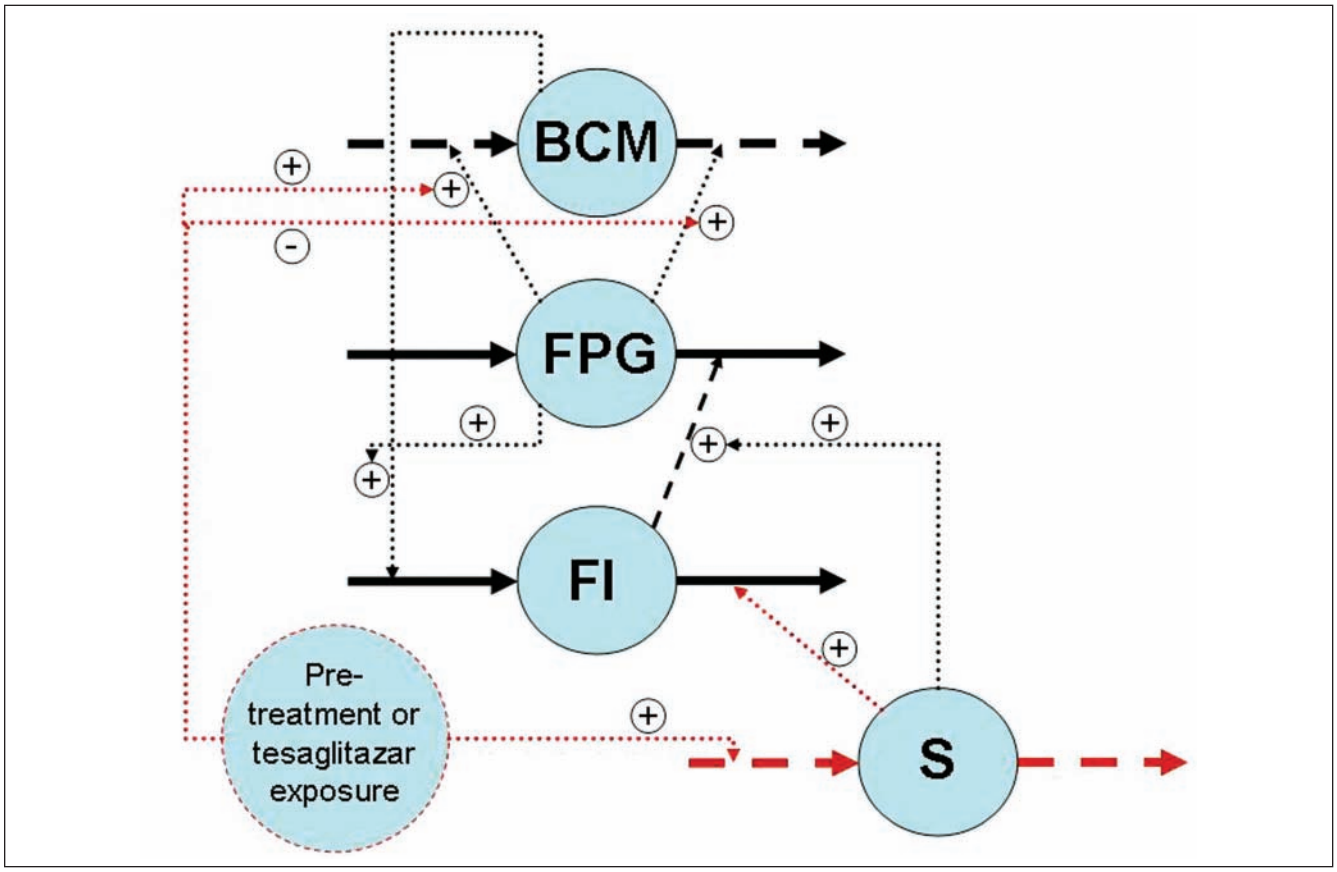


*Figure 3. Schematic illustration of the semi-mechanistic fasting plasma glucose–fasting insulin (FPG-FI) model, incorporating insulin sensitivity (S) and beta-cell mass (BCM). Changes from the steady state are illustrated as indirect effects for all 4 variables, indicated by solid or broken arrows. However, responses in FPG and FI are relatively fast and therefore assumed at steady state relative to one another, at the given level of S and BCM. Drug treatment exerts an indirect effect on S and BCM, which explains the delay in the response of FI and FPG. The indirect effects of drug treatment and the relation between S and insulin clearance are additions to the model from that originally suggested by Topp et al.[9] This has been indicated by the gray (online: red) line color.*

available in data. The parameter variability within a DGR was distributed according to

$$P_i = TVP_i \cdot \exp(\eta_{Pi}), \quad (6)$$

where $P_i$ is the individual parameter, $TVP_i$ is the typical parameter value (typical for all subjects or for the specific DGR), and $\eta_{Pi}$ is assumed having a normal distribution centered around zero with standard deviation $\omega_P$ representing the interindividual variability (IIV).

The effect of tesaglitazar on $S_i$ was described according to an $E_{max}$ model,

$$E_{Sit} = \frac{E_{max_{Si}} \cdot C_{it}}{EC50_{Si} + C_{it}}, \quad (7)$$

where $C_{it}$ is the plasma concentration of tesaglitazar in individual i at time t, $E_{maxSi}$ is the maximum response to tesaglitazar, and $EC50_{Si}$ is the concentration producing half-of-maximum response on $S_i$. For the effect of tesaglitazar on OFFSET ($E_{Bit}$), the initial nonsigmoidal $E_{max}$ model estimated the typical value of $E_{max}{}^{B}$ slightly larger than 1. Assuming $E_{max} = 1$ for a sigmoid-$E_{max}$ model fit data better, according to

$$E_{Bit} = \frac{C_{it}^{\gamma_B}}{EC50_{Bi}^{\gamma_B} + C_{it}^{\gamma_B}}, \quad (8)$$

where $\gamma_B$ is the factor determining the sigmoidicity. Because $E_{Bit}$ >1 would be unreasonable for any individual (cf. equation 4) a logit transformation was used to restrict the individual pretreatment effect (see Online Appendix Part 3, OA3).

### Model Evaluation

In addition to standard goodness-of-fit graphs, the model was evaluated using nonparametric bootstrap[27] and visual-predictive check (VPC),[28] including both median biomarker profiles over time and the distribution of observations. For VPC, a graphical comparison was made between observed data and the model-predicted median and 95% prediction interval (95% PI) over time. The Online Appendix Part 2 (OA2) elaborates on more technical details of model fitting and selection, including details of the residual error model.

## RESULTS

The model could accurately describe the observed FPG and FI data over time and provided plausible projections of BCM adaptation and $S_{it}$ following tesaglitazar treatment. Final model parameter estimates are presented in Table II. All T2DM patients have deterioration in BCM and S compared to the normal subject. The typical subject in the SIR study (DGR 1) has slightly reduced S and FPG above normal. The 4 groups of T2DM patients typically have an S that is reduced by 37% to 50% and FPG elevated by 3.1 to 3.9 mmol/L over the normal 5.6 mmol/L. The dynamic change in S was relatively fast, and new steady state is expected after approximately 6 weeks of treatment.

Insulin sensitivity increased almost proportional to tesaglitazar exposure (indicated by the high $EC50_S$), whereas the treatment effect on BCM (OFFSET) has nearly reached its maximum at the higher doses (2 and 3 mg tesaglitazar). Consequently, increasing the dose from 1 to 3 mg would lower FI considerably but FPG less. However, the effect on BCM (OFFSET) is highly variable between patients, as indicated by the high IIV in $EC50_B$ (>100%). Therefore, some patients would require substantially higher exposure for the same BCM-mediated effect on FPG. The model describes correlations in the individual parameter values, which can not be explained by DGR or drug exposure: subjects who have low insulin sensitivity tend to have higher OFFSET (ie, higher FPG), and patients who respond well to drug treatment with respect to insulin sensitivity also respond well in terms of BCM adaptation (i.e. FPG).

Figure 4 compares the model predictions of FPG and FI to the observations in the naive patients in the GLAD study who were given 0.5 to 3 mg of tesaglitazar. Figure 5 shows the subjects in the SIR study treated with 0.5 or 1 mg tesaglitazar. In both figures, the median and 95% confidence interval of data are predicted fairly well at all time points. The total data contain 21 unique combinations of DGR and tesaglitazar dose. The model describes FPG and FI well in all of these, as can be seen from the 2 figures in OA2.

In Figure 6, the model predictions for FPG, FI, S, and BCM for each of the 5 DGR are depicted for a hypothetical 42-week study with 1 mg tesaglitazar. Insulin sensitivity improved rapidly and greatly in both insulin-resistant subjects and patients with T2DM, which is expected given the PPAR $\alpha/\gamma$ activation. As a consequence of the improved S, FI is greatly reduced during the first few weeks of treatment. In T2DM patients (DGR 2-5), a small rebound in FI was predicted due to beta-cell adaptation. BCM reached a new steady state after about 6 months of treatment. In insulin-resistant subjects, there is a fast improvement in S and FI but little effect on FPG.

The NONMEM model code for fitting the model to data (ie, estimate model parameters) is available in OA3.

## DISCUSSION

In this article, we have developed a semi-mechanistic model for the interaction between tesaglitazar exposure, FPG, FI, S, and BCM. The model described all observations well, even though data originated from heterogeneous populations, ranging from insulin-resistant subjects to T2DM patients at different disease stages. The foundation of this model has previously been suggested by Topp et al.[9] However, before the present work, their model had not been assessed in a diabetic population; instead, it is derived from different sources in literature.

In the new PKPD model, patients with T2DM were assumed to differ from normal subjects only by an offset in the beta-cell adaptation (ie, lower BCM) and lower insulin sensitivity coupled to lower insulin clearance. This limitation was necessary given the complexity of the model in combination with the fact that only fasting observations were available. The maximal insulin secretion rate ($\sigma$) could not be separated from the variable BCM because the latter was not measured. Therefore, BCM predicted from the model should be seen as a functional mass, reflecting the actual mass only if *fasting* $\sigma$ is the same for patients and healthy individuals. However, the relative difference in BCM between normal

**Table II** Parameter Estimates of the Semi-Mechanistic FPG-FI Model

| **Parameter values from literature representing a normal subject, according to Topp et al[9]** | | |
|---|---|---|
| **Parameter** | **Estimate** | **RSE, %** |
| S, L $pmol^{-1}$ $d^{-1}$ | 0.104 | — |
| $R_0$, mmol $L^{-1}$ $d^{-1}$ | 1.44 | — |
| $E_{G0}$, $d^{-1}$ | 48.0 | — |
| σ, pmol $L^{-1}$ $d^{-1}$ | 300 | — |
| α, mmol $L^{-1}$ | 7.85 | — |
| k, $d^{-1}$ | 432 | — |
| $d_0$, $d^{-1}$ | 0.06 | — |
| $R_1$, L $mmol^{-1}$ $d^{-1}$ | 0.0151 | — |
| $R_2$, $L^2$ $mmol^{-2}$ $d^{-1}$ | 0.000779 | — |
| **Parameter values as estimated from SIR, GLAD, and GALLANT6** | | |
| **Parameter** | **Estimate** | **RSE, %[a]** |
| S, L $pmol^{-1}$ $d^{-1}$ | 0.0842/0.0660/0.0524/0.0654/0.0626[b] | 2/5/6/4/3 |
| OFFSET, mmol $L^{-1}$ | 0.199/3.12/3.51/3.92/3.08[b] | 13/3/4/3/3 |
| $k_{out}$, $d^{-1}$ | 0.0599 | 7 |
| $REL_{k\text{-}S}$ | 0.653 | 3 |
| $pret_B$, % reduction | 27.0/52.6[c] | 8/4 |
| $pret_S$, % increase | 19.6 | 19 |
| $E_{max}S$, % | 948 | 30[d] |
| $EC50_S$, μmol $L^{-1}$ | 7.43 | 35[d] |
| $EC50_B$, μmol $L^{-1}$ | 0.463 | 6 |
| $\gamma_B$ | 1.12 | 8 |
| $\theta_{HOFFSET}$, mmol $L^{-1}$ | 1.64 | 11 |
| **Interindividual variability, IIV[e]** | | |
| $\omega_S$, % | 56.6 | 3 |
| $\omega_{OFFSET}$, % | 26.0/38.7[f] | 7/5 |
| $\omega_{pretB}$, % | 81.6/53.0[g] | 14/13 |
| $\omega_{EC50S}$, % | 48.4 | 9 |
| $\omega_{EC50B}$, % | 104 | 10 |
| $\omega_{resFPG}$, % | 47.2 | 3 |
| $\omega_{resFI}$, % | 24.0 | 7 |
| Cor(S,OFFSET) | –0.372 | 6 |
| Cor($EC50_S$, $EC50_B$) | 1 | — |
| Cor($RES_{FPG}$, $RES_{FI}$) | 0.696 | 9 |
| **Residual error magnitude for the typical individual** | | |
| $RES_{FPG}$, % | 8.00 | 1 |
| $RES_{FI}$, % | 30.9 | 2 |

FPG, fasting plasma glucose; FI, fasting insulin; RSE, relative standard error; SIR, Study in Insulin Resistance; GLAD, Glucose and Lipid Assessment in Diabetes.

[a]Calculated by the bootstrap standard deviation relative to the point estimate.

[b]Parameter values have been estimated separately for each of disease groups (DGR) 1 to 5.

[c]Parameter values have been estimated separately for GLAD and GALLANT6.

[d]The ratio of $E_{max}S$ and $EC50_S$ was estimated with 5% RSE.

[e]The IIV is given as coefficient of variation (CV) and the correlation between random components as the Pearson-correlation coefficient.

[f]Parameter values have been estimated separately for drug-naive and pretreated patients (ie, DGR 1-3 and 4-5, respectively).

[g]Only one parameter was estimated for $\omega_{pretB}$. The 2 IIVs are due to a logit transformation of the individual parameter distribution in combination with different typical values for $pret_B$ for GLAD and GALLANT6.

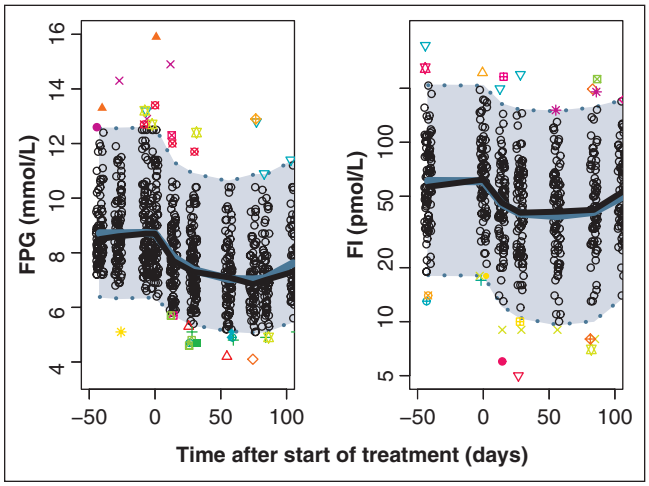


*Figure 4. Visual predictive check of fasting plasma glucose (FPG) and fasting insulin (FI) on the semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model, evaluated on the naive patients in GLAD (DGR 2) who were randomized to 0.5, 1, 2, or 3 mg tesaglitazar. The black and gray (online: blue) solid lines represent observed and model-predicted median, respectively. The light gray (online: light blue) area within the dotted line represents the model 95% prediction interval (PI). The black circles represent observations within the PI, and observations outside the PI are represented by a nonblack plotting symbol that is unique for each individual. The observed median and 95% confidence interval are both described well by the model. The observations have been jittered in the horizontal direction. As seen from the right panel, FPG decreases over the whole treatment period as a result of increased insulin sensitivity and increasing beta-cell mass (BCM). FI, on the other hand, first decreases due to increasing insulin sensitivity but then displays a small rebound, as insulin sensitivity has reached treatment steady state and the adaptation of BCM is still ongoing.*

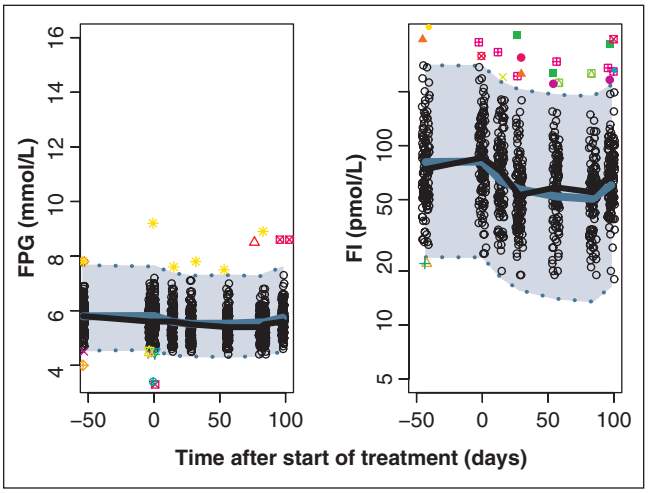


*Figure 5. Visual predictive check of fasting plasma glucose (FPG) and fasting insulin (FI) on the mechanistic pharmacokinetic-pharmacodynamic (PKPD) model, evaluated on the insulin resistant subjects in SIR (DGR 1) who were randomized to 0.5 or 1 mg tesaglitazar. Legend as in Figure 4. As seen from the left panel, FPG is not much affected when treating nondiabetic subjects. FI, on the other hand, decreases due to increasing insulin sensitivity. The observed median is described well, but the 95% confidence interval is slightly overpredicted by the model. The observations have been jittered in the horizontal direction. (Figures online are in color.)*

subjects (DGR 0) and patients with T2DM (DGR >1) is in line with previous autopsy data.[22-25]

Although the model by Topp et al[9] is apt to handling both fasting and postprandial data, their focus is on fasting dynamics. Consequently, by including clinical-experimental studies, our model may need expansion (eg, by describing the acute-phase insulin secretion and the deterioration of this response in insulin-resistant subjects and diabetic patients).[29,30] Including clinical-experimental studies and observations of the BCM[31] may enhance the model, making it less reliant on parameters suggested by Topp et al.[9] However, we would also like to emphasize a positive consequence of relying on their parameter values. Our model does not estimate the rate of BCM adaptation rate. Instead, this is completely determined by the parameter values from Topp et al[9] in combination with the offset model we extended to their model for describing diabetic patients. The fact that our model matches the observed FPG dynamics well supports both the parameter values provided by Topp et al[9] and our implementation of increasing set point with diabetes. Moreover, the fixed adaptation rate admits decoupling of beta-cell adaptation over the first 6 months of treatment and the long-term disease progression, so that the latter may possibly be assessed with better precision, even in studies with limited treatment duration (1-2 years).

The model structure described by Topp et al[9] and further developed here is referred to as *semi*-mechanistic. The 4 main reasons for this are discussed as follows. First, Topp et al[9] placed the insulin effect on glucose elimination and not on glucose production (Figure 3 and equation 9 in OA1). This can be regarded as a mechanistic description of glucose control after a meal, but during fasting, the main action of insulin is on glucose production. Second, the incorporation of beta-cell dynamics is an important mechanistic improvement compared to other models for glucose dynamics but can be improved further compared to the

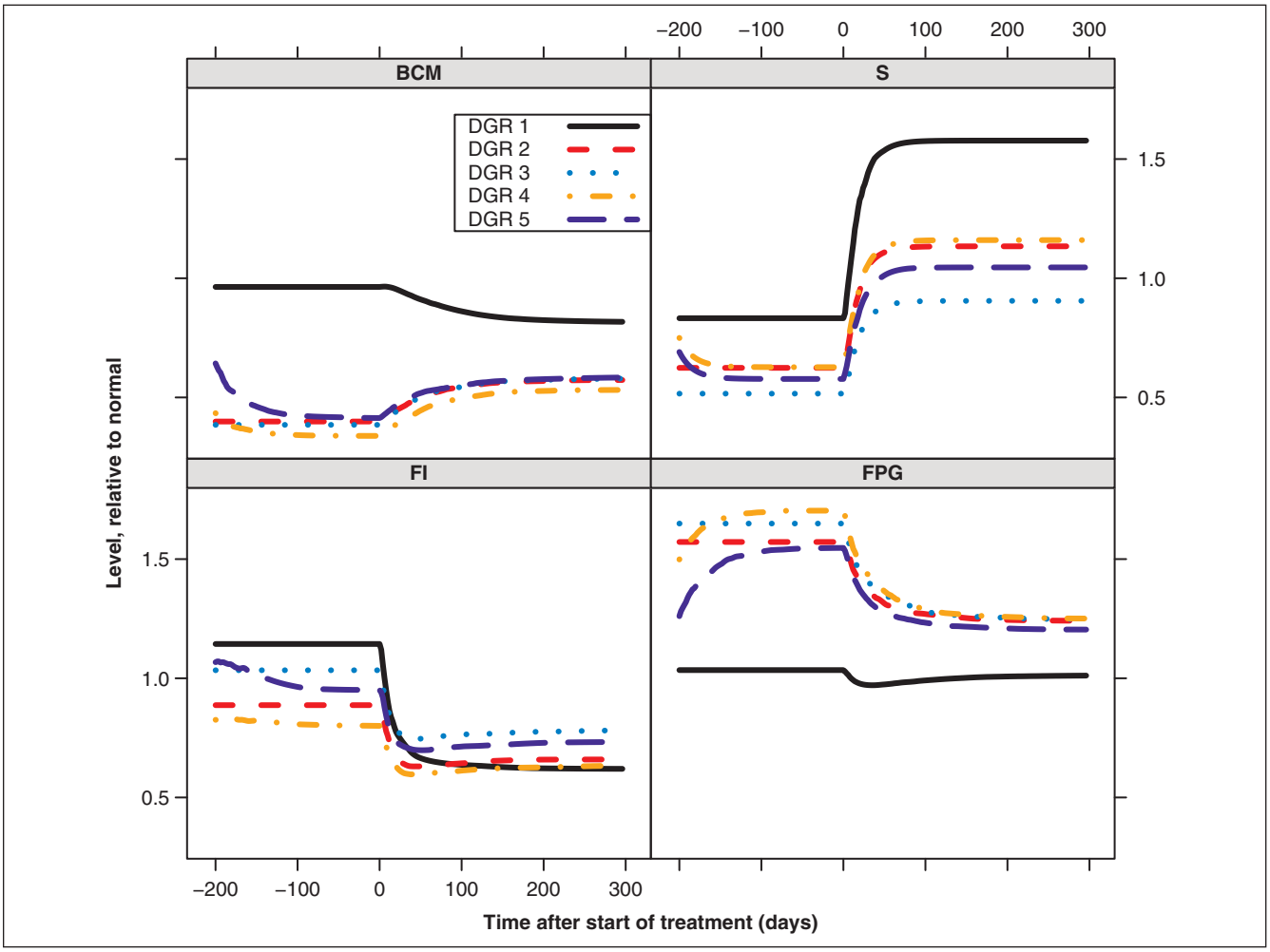


*Figure 6. The change in beta-cell mass (BCM), insulin sensitivity (S), fasting insulin (FI), and fasting plasma glucose (FPG) simulated by the mechanistic pharmacokinetic-pharmacodynamic (PKPD) model using a fictitious study design, including all 5 disease groups (DGR). The median response to 1 mg daily dosing of tesaglitazar is displayed. DGR 1 has a normal BCM, whereas the diabetic patients have only 40% to 60% of this at the start of the run-in. Treatment increases the BCM in the diseased but not in DGR 1, where the increased S even forces the adaptation in the other direction. Right before the treatment is commenced, the underlying disease is seen, due to the long duration of the run-in period. If the patients were to be left untreated in this manner, DGR 3 has the lowest S, whereas DGR 4 has the lowest BCM. (Figures online are in color.)*

current use of a polynomial (Figure 2 and equation 11, OA1). Third, regarding the saddle point, where a disturbance of the glucose regulation can push a T2DM patient into a state that will lead to severe deterioration of BCM (accelerated glucose toxicity), this mechanism may be part of the manifestation of diabetes mellitus but is unlikely to occur in a study with T2DM patients. Simply estimating different parameter values in equation (11) (BCM regulation) for T2DM patients would put some patients dangerously close to the saddle point: without the offset model that we implemented, simulations from such a model would result in a fraction of patients temporarily becoming insulin dependent as a consequence of run-in or placebo. Last, because only one parameter can be estimated for how BCM adaptation differs between T2DM patients and healthy subjects, our approach was to incorporate an offset in the glucose level toward which BCM is adapting. The offset model relies on that assumption and can be justified only by the model describing the observed clinical data well. Most recently, De Gaetano et al[32] suggested a model supposedly improving that of Topp et al[9] but again not fitting

the model to any observational data. The model structure in De Gaetano et al[32] may provide substantial improvements in describing glucose toxicity and its effect on disease progression and is a step in the direction of more mechanistic models.

The model identified a strong relation between insulin sensitivity and insulin clearance, which has been reported earlier with PPARs.[17-19] Both of these processes are affected by the level of nonesterified fatty acid (NEFA), which is reduced by tesaglitazar treatment.

Using a population modeling approach, within-subgroup variability was separated into interindividual variability in the parameters and residual variability in FPG and FI. On the individual level, there was high correlation between the drug effects on insulin sensitivity and the FPG set point (ie, $EC50_{Si}$ and $EC50_{Bi}$). This may be because the 2 effects share the same mechanistic pathways or because improved insulin sensitivity reduces glucose toxicity. Possibly, beta-cell adaptation is affected by NEFA due to lipotoxicity.[12,33,34] However, the clinical implications of this mechanism remain to be established.[35]

The interest in mechanistic models is growing with the increasing use of quantitative pharmacology.[1,36-41] The benefits of using more mechanistic models include the possibility of analyzing a wide range of studies and populations under the same model, increased knowledge about the drug and disease, and better model predictions of previously unexplored populations or study conditions. By including model components describing longitudinal disease progression on BCM and insulin sensitivity, the predictions of 10-year outcomes can likely become more accurate than performed by earlier models.[2,4] With such components, the model can separate gradual disease progression from the symptomatic effects on beta-cell adaptation and insulin sensitivity, which is of interest because treatment may affect disease progression in a protective (or destructive) way.[4] However, this requires data from longer studies than available in the current analysis.

In conclusion, we have developed a semi-mechanistic PKPD model describing the dynamics of FPG, FI, S, and BCM and the effect of treatment on this system. Model predictions that cannot be assessed on available data are well supported by the literature (eg, 40% of normal BCM in untreated T2DM patients[22-25] and a positive relation between insulin sensitivity and insulin clearance). The model may benefit from further development using even more heterogeneous data. The role of NEFA may be investigated not only on the mechanistic pathway to insulin sensitivity and insulin clearance[17-19] but also to BCM.[12,33,34] Clinical-experimental studies may reduce the dependence on the parameter values from Topp et al.[9] Finally, as it becomes possible to quantify BCM in vivo, longitudinal measurements of this biomarker may enhance the model.

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