Evaluation of a mathematical model of diabetes progression against observations in the Diabetes Prevention Program

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Hardy T, Abu-Raddad E, Porksen N, De Gaetano A. Evaluation of a mathematical model of diabetes progression against observations in the Diabetes Prevention Program. Am J Physiol Endocrinol Metab 303: E200–E212, 2012. First published May 1, 2012; doi:10.1152/ajpendo.00421.2011.—The seminal publication of the Diabetes Prevention Program (DPP) results in 2002 has provided insight into the impact of major therapies on the development of diabetes over a time span of a few years. In the present work, the publicly available DPP data set is used to calibrate and evaluate a recently developed mechanistic mathematical model for the long-term development of diabetes to assess the model’s ability to predict the natural history of disease progression and the effectiveness of preventive interventions. A general population is generated from which virtual subject samples corresponding to the DPP enrollment criteria are selected. The model is able to reproduce with good fidelity the observed time courses of both diabetes incidence and average glycemia, under realistic hypotheses on evolution of disease and efficacy of the studied therapies, for all treatment arms. Model-based simulations of the long-term evolution of the disease are consistent with the transient benefits observed with conventional therapies and with promising effects of radical improvement of insulin sensitivity (as by metabolic surgery) or of β-cell protection. The mechanistic diabetes progression model provides a credible tool by which long-term implications of antidiabetic interventions can be evaluated.

The pathophysiology of type 2 diabetes mellitus (T2DM) involves both reduced insulin responsiveness in target tissues (i.e., insulin resistance) and inappropriately reduced insulin secretion in the setting of hyperglycemia. The latter defect, in turn, may depend on both functional abnormalities of the pancreatic β-cells and an absolute decrease in the number of these cells. In most individuals, the development of insulin resistance and the loss of β-cell function likely develops over many years and reflects genetic and environmental influences that differ widely among affected individuals.

Whatever the genetic or environmental determinants, the interplay of insulin resistance, decreased pancreatic β-cell responsiveness, and β-cell population dynamics alterations determines at first a slowly increasing glycemia, compensated in the early phases of the disease by increased circulating insulin levels. This compensatory process is known to involve an expansion of β-cell mass in rodents (4, 5), and similar conclusions can be drawn from studies of human autopsy specimens (6). In more advanced stages of the disease, a deficit of β-cells develops. The cause of this defect is still not completely clear, but the role of glucose toxicity on β-cell replication/apoptosis rates has been strongly advocated (21).

When the compensation mechanisms fail, glycemia climbs rapidly, and the frank clinical picture of diabetes emerges (23). This sequence of events appears to underlie the progression from the normal state to the prediabetic states of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) to frank T2DM.

The slow and variable progression of T2DM poses a significant challenge to the experimental evaluation of its natural history and to the testing of interventions that may alter progression of this disease. Mathematical models of disease offer an opportunity to simulate disease progression where long-term clinical observations may be lacking and to explore in silico the effects of various interventions. Mechanistic models for the progression of diabetes (8, 36) attempt to coherently integrate commonly accepted physiological mechanisms to predict the long-range behavior of disease processes and offer an opportunity for specifying unambiguously the assumptions made as well as to demonstrate formally the qualitative consequences that follow from these assumptions. Other mathematical models have also been proposed for the representation of the long-term interaction of the β-cell population, fasting plasma glucose (FPG), and fasting serum insulin (FSI) in the development of T2DM (9) or as discrete-state dynamical systems with covariate-dependent transition probabilities among states (11, 32, 40).

Recently, we described the development of the Diabetes Progression Model (DPM) (8), which utilizes a combination of differential and algebraic equations to recapitulate the pathophysiological processes involved in T2DM over the long term (i.e., months or years). DPM explicitly represents phenomena involved in glucose homeostasis such as glucose-dependent insulin secretion, insulin-mediated glucose disposal, short-term stimulation, and long-term depression of insulin production by hyperglycemia (glucose toxicity). This model allows simulation of progressive worsening of insulin resistance and the resulting changes in β-cell mass. The latter may result from alterations in replication or apoptosis rates due to glucose toxicity or other processes. It is anticipated that mathematical models may be used to test hypotheses about the natural history of the disease and about the effects of different therapeutic schemes. A valid disease and therapeutic model could be used to inform clinical trial design; for example, decisions about study population, sample size, and treatment duration can be based on model simulations and predicted interactions between drug mechanisms and disease progression.

A fundamental question preliminary to the practical use of such models concerns their validation against known medium-term disease progression data. In the present work, we have evaluated the performance of the DPM by assessing its ability...
to accurately predict the results of the Diabetes Prevention Program (DPP) study (19, 20). This hallmark study examined the incidence of new-onset diabetes in an “at-risk” group treated with intensive lifestyle intervention, metformin, troglitazone, or routine care. The DPP data set provides a useful term of comparison against which to test the ability of the DPM to recapitulate the natural history of T2DM and the impact of lifestyle or pharmacological interventions.

**METHODS**

**DPP data set.** The objectives and results of the DPP study have been described previously (19, 20). Briefly, this study evaluated the incidence of T2DM in an at-risk population randomized to placebo (n = 1,082), intensive lifestyle modification (n = 1,079), metformin (n = 1,073), or troglitazone (n = 585). From 1996 to 1999, the study enrolled adult subjects with elevated FPG (from 5.6 to 7.7 mmol/l before June 1997 and from 5.3 to 6.9 mmol/l after June 1997) and 2-h glucose (G2h; from 7.8 to 11.0 mmol/l) during a 75-g oral glucose tolerance test (OGTT) as well as elevated body mass index (BMI ≥22 kg/m²) in Asians, BMI ≥24 kg/m² otherwise).

The average followup for individuals in the placebo, lifestyle (indicated as ILS in the original publication), and metformin groups was 2.8 yr (19), whereas the average length of treatment with troglitazone was 0.9 yr as a result of its withdrawal from the market (20). Diabetes was diagnosed on the basis of an annual OGTT or a semiannuual FPG test using the following criteria: FPG ≥7.0 mmol/l or G2h ≥11.1 mmol/l. In the present work, only the fasting glucose criterion was used to define new-onset diabetes, because the present version of the DPM is not constructed to simulate postchallenge glycemia (vide infra). Fifty-nine subjects had FPG >7 mM at entry and were excluded from the present analysis. A total of 3,606 subjects over the four protocol arms were thus available for analysis. Summary statistics for demographic and baseline glycemic parameters calculated from this data set were in close agreement with the corresponding published statistics [Table 1 and original DPP data set (not shown)]. The DPP data set was obtained on request from the National Institute of Diabetes and Digestive and Kidney Diseases (February 2008 Full Scale data release, data request no. 608).

**Model structure.** The DPM is described in detail elsewhere (8). Briefly, it consists of a system of differential and algebraic equations describing the simultaneous evolution of β-cell mass, pancreatic β-cell replication reserve, prevailing glycemia, and prevailing insulinemia on the basis of parameters representing, among other things, insulin-dependent tissue glucose uptake, hepatic net glucose output, β-cell insulin secreting ability, and insulin elimination from plasma (Table 1).

The DPM focuses on long-term evolution (in the “slow time” of months or years), making no attempt to represent short-term variations in glycemia and insulinemia over minutes to hours (such as those following meal ingestion), and does not currently discriminate between central (liver) and peripheral (muscle and fat tissue) sensitivity to insulin. Model parameter estimates were obtained primarily from published human data, as described previously (8). The model assumes a spontaneous decrease in insulin sensitivity (parameter KxgI), starting from a normal value in early life ($1.0 \times 10^{-4} \text{min}^{-1}, \text{pM}^{-1}$), based on normative data from frequently sampled intravenous glucose tolerance test measurements (1, 15, 28), represented as a sigmoidal monotonically decreasing curve. The steepness of this decrement may be set to reflect diverse individual time courses ranging from essentially maintained insulin sensitivity into old age to early development of a severe degree of insulin resistance. This is described further below.

The “prevailing” glycemia and insulinemia levels described in the model do not refer strictly to either fasting or postprandial values but are in fact representative of daily steady-state blood concentrations, hourly oscillations being averaged out when considering the evolution of the system over a time span of months or years. Prevailing glycemia and insulinemia are derived as equilibrium values, given the existing level of insulin sensitivity and the current functional β-cell mass available for insulin secretion; they substantially reflect real-life postabsorptive values and correspond to the FPG values in the DPP data set.

In the model, changes in β-cell population size depend on prevailing glycemas via a direct short-term stimulation and an indirect longer-term inhibition of net replication due to glucose toxicity “exhausting” β-cell net replication reserve. For the current analysis, we introduced a minor modification to the original model by representing β-cell growth with a logistic rather than an exponential growth function; therefore, the equation for β-cell mass reads [using the same nomenclature as in DeGaetano et al. (8)]

$$\frac{dB(t)}{dt} = d(GB)B \left(1 - \frac{B}{B_{max}} \right), \quad B(t_0) = B_0.$$  

**Patient simulations.** The simulation procedure was started by a random generation of several thousand subjects differing in initial glycemia, rate of development of insulin resistance, and age at enrollment; given eventual enrollment percentages of 6–8%, about 15,000 simulated subjects produced an enrolled simulated sample of 1,000 subjects. Simulated subjects differ from one another in only three parameters [Gluc0, t0, and $\nu_1$; notice that Gluc0 (8) has been renamed Gluc0, for clarity], with the remaining parameters being fixed at the values assessed in previous work (8) and reported in Table 2. These three parameters, which have been made to vary independently for the present set of simulations, express the “baseline” prevailing glycemia in early life (Gluc0), the time of 50% decrease from normal insulin sensitivity (t0), and the steepness of the insulin sensitivity decrease over time ($\nu_1$), represented as a sigmoidal function. Taken together, these three parameters describe the life history of the variation of insulin sensitivity in the given subject; in this sense, they incorporate the effect of conditions commonly associated with varying risk of progression of insulin resistance, such as BMI, sex, ethnicity, genetic predisposition, or (spontaneous) lifestyle. Different combinations of the values of these three parameters give rise to insulin sensitivity curves, which may range from essentially normal values maintained throughout old age to severe insulin resistance occurring in early years. Furthermore, different values of these pa-

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**Table 1. Comparison of observed (DPP) and SIM populations (key parameters at baseline)**

<table>
<thead>
<tr>
<th></th>
<th>DPP</th>
<th>SIM</th>
<th>DPP</th>
<th>SIM</th>
<th>DPP</th>
<th>SIM</th>
<th>DPP</th>
<th>SIM</th>
<th>DPP</th>
<th>SIM</th>
</tr>
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<tr>
<td><strong>Placebo</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. studied</td>
<td>1,082</td>
<td>1,000</td>
<td>1,079</td>
<td>1,000</td>
<td>1,073</td>
<td>1,000</td>
<td>585</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at enrollment, yr</td>
<td>50.3 ± 10.4</td>
<td>50.48 ± 10.05</td>
<td>50.6 ± 11.3</td>
<td>50.39 ± 10.23</td>
<td>50.9 ± 10.3</td>
<td>50.3 ± 10.47</td>
<td>51</td>
<td>50.75 ± 10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glycemia at enrollment, mM</td>
<td>5.92 ± 0.47</td>
<td>5.92 ± 0.42</td>
<td>5.90 ± 0.45</td>
<td>5.92 ± 0.42</td>
<td>5.92 ± 0.47</td>
<td>5.92 ± 0.42</td>
<td>6.7</td>
<td>8.2</td>
<td>5.96</td>
<td>5.92 ± 0.42</td>
</tr>
<tr>
<td>%Enrolled</td>
<td>8.5</td>
<td></td>
<td></td>
<td></td>
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</table>

DPP, Diabetes Prevention Program; SIM, simulation.
parameters may give rise to glycemic curves that increase more or less rapidly starting from a relatively narrow range of glycemia at enrollment. As a simple example, we may think of increasing both $\tau_1$ and $\tau_2$ to obtain a steeper increase in glycemia from the same enrollment glycemia at a given age. Computer simulations were used to empirically identify a distribution of $\text{Gluc}_0$, $t_0$, and $\tau_1$ that would reproduce both the DPP-observed distribution of enrollment glycemia and the DPP-observed glycemia increases after enrollment in the placebo group. It must be underscored that none of the treatment-related outcomes were premodeled in the calibration phase.

Virtual subjects were allowed to progress (i.e., “age”) following the DPM model, and a sample of subjects whose entry characteristics matched the DPP enrollment criteria was selected on the basis of measured $\text{Gluc}_0$, $t_0$, and $\tau_1$ that would reproduce both the DPP-observed distribution of enrollment glycemia and the DPP-observed glycemia increases after enrollment in the placebo group. The effect size was expressed as peak effect in percent of untreated diabetic values up that visit.

### Effect of therapy.
All interventions (diet and exercise, metformin, or troglitazone) were assumed to impact glucose homeostasis only through effects on insulin sensitivity. For each treatment scheme, the effect of intervention, expressed as a proportional shift from the natural time course of insulin sensitivity, was simulated as a difference of exponentials, with size and rate parameters determining the magnitude and the rapidity of onset and decay of the effect. Starting with assumptions based on the authors’ experience regarding the clinical effects of these agents, multiple simulations were performed to empirically determine these parameters for each group with the goal of matching simultaneously the time course of average glycemia and of cumulative incidence of FPG $>7$ mM from the DPP data set. Random variation among subjects with respect to the systematic effect of therapy was incorporated as well as random scatter of observed glycemia around the (smooth) model-predicted time course. For the metformin arm, a single difference-of-exponentials time course of effect was not sufficient to match satisfactorily the observed average glycemia, and therefore, the combination of two such effects (one faster, one slower) was employed.

The effect size was expressed as peak effect in percent of untreated diabetic values. In other words, each individual virtual subject’s unmodified time course of insulin sensitivity was computed over the entire study period. This “natural” time course of insulin sensitivity was then incremented proportionally over the treatment period by the individual effect size, the average of which over the many subjects is reported.

More precisely, the time course of “natural” insulin sensitivity over the lifetime of the subject was modeled as cumulative incidence at the previous visit time plus the product of diabetes incidence at each visit times the residual fraction of nondiabetics up to that visit.

### Table 2. Parameter values used in simulations

<table>
<thead>
<tr>
<th>Parameter and Unit</th>
<th>Meaning</th>
<th>Placebo</th>
<th>Lifestyle</th>
<th>Metformin</th>
<th>Troglitazone</th>
</tr>
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<tbody>
<tr>
<td>$\text{Bcel}_0$</td>
<td>Million $\beta$-cells at $t_0$</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Bmax, } \text{Mc}$</td>
<td>Maximal $\beta$-cell population</td>
<td>4,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Gluc}_0$</td>
<td>Glycemia at $t_0$, mM</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Insu}_0$</td>
<td>Insulinemia at $t_0$, pM</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{KetaG}$</td>
<td>Glucose toxicity coefficient $\cdot$ mo$^{-1}$ $\cdot$ mM$^{-1}$</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{eta}_0$</td>
<td>Baseline pancreatic reserve/mo</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$\text{Gluch}$</td>
<td>Glycemia of 50% pancreatic insulin release, mM</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$\text{Nih}$</td>
<td>Steepness of Hill function glucose-driven pancreatic insulin release (no.)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_{\text{nil}}$</td>
<td>Minimal $\beta$-cell replication rate/mo</td>
<td>$-0.02$</td>
<td></td>
<td></td>
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<tr>
<td>$K_{\text{xu}}$</td>
<td>$\text{Hb} \Delta_1$, elimination rate/mo</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$\text{Hb } \text{A1c, } %$</td>
<td>Baseline $\text{Hb} \Delta_1$</td>
<td>5</td>
<td></td>
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<tr>
<td>$K_{\text{etl0}}$</td>
<td>Baseline (normal) insulin sensitivity $\cdot$ min$^{-1}$ $\cdot$ pM$^{-1}$</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$K_{\text{etlmin}}$</td>
<td>Fractional minimal achievable insulin sensitivity (no.)</td>
<td>0.025</td>
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<tr>
<td>$\eta_1$</td>
<td>Time at 50% decrement of insulin sensitivity in months before enrollment</td>
<td>$-125$</td>
<td></td>
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<tr>
<td>$\text{nil}$</td>
<td>Steepness of Hill-function decrement in insulin sensitivity (no.)</td>
<td>18</td>
<td></td>
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<tr>
<td>$K_{\text{xu}}$, $\text{start}$</td>
<td>Baseline insulin elimination rate/min</td>
<td>0.05</td>
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<tr>
<td>$K_{\text{xu}}$, $\text{end}$</td>
<td>End-of-life insulin elimination rate/min</td>
<td>0.035</td>
<td></td>
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<tr>
<td>$\text{Tre}t\text{a End}$</td>
<td>End-of-life pancreatic reserve restoration rate as a fraction of (normal) baseline value (no.)</td>
<td>0.94</td>
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<tr>
<td>$K_{\text{etg}}$</td>
<td>Insulin-independent 1st-order glucose elimination rate/min</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$\text{MetDose}$</td>
<td>Peak effect of metformin (part 1 of 2) as proportion of current insulin sensitivity (no.)</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>$\text{Metformin-} \alpha$</td>
<td>Rate of increase of effect (no.)</td>
<td>0.015</td>
<td></td>
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<tr>
<td>$\text{Metformin-} \beta$</td>
<td>Rate of decrease of effect (no.)</td>
<td>0.008</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$\text{LiSt dose}$</td>
<td>Peak effect of lifestyle, placebo, troglitazone, or metformin (part 2 of 2) as proportion of current insulin sensitivity (no.)</td>
<td>0.035</td>
<td>0.5</td>
<td>0.3</td>
<td>0.48</td>
</tr>
<tr>
<td>$\text{LiSt-} \alpha$</td>
<td>Rate of increase of effect (no.)</td>
<td>0.06</td>
<td>0.08</td>
<td>0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>$\text{LiSt-} \beta$</td>
<td>Rate of decrease of effect (no.)</td>
<td>0.03</td>
<td>0.026</td>
<td>0.03</td>
<td>0.024</td>
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</table>
\[ \tilde{K}_{xgl} = \begin{cases} K_{xgl0} (1 - (1 - K_{xgl, min}) (t - t_0)^{y_1})/(t_1 - t_0)^{y_1} + (t - t_0)^{y_1}, & t \geq t_0, \\ K_{xgl0}, & t \leq t_0, \end{cases} \]

where \( K_{xgl, min} \) is a proportional minimum bound on \( K_{xgl} \), set at 0.025.

To this natural time course an effect of therapy was added, producing the actual operating value of insulin sensitivity at any given time:

\[ K_{xgl} = \tilde{K}_{xgl}(1 + Metf + List + Tzd). \]

The effects of therapy were modeled by means of sums of exponentials, for instance,

\[ Metf = \begin{cases} 0, & \text{if } t < t_{\text{Metf}} \\ \frac{\text{MetfDose} \cdot \text{Peak}(\alpha_{\text{Metf}}, \beta_{\text{Metf}})}{(e^{-\beta_{\text{Metf}}(t - t_{\text{Metf}})} - e^{-\alpha_{\text{Metf}}(t - t_{\text{Metf}}))}}, & \text{otherwise,} \end{cases} \]

where MetfDose is actually expressed as proportional peak effect of therapy on insulin sensitivity and

\[ \text{Peak}(\alpha, \beta) = (e^{-\beta(t_{\text{peak}})} - e^{-\alpha(t_{\text{peak}})}), \]

\[ t_{\text{peak}} = \frac{\log(\alpha/\beta)}{\alpha - \beta}. \]

An additional series of simulations was performed to visualize the observable diabetes incidence rates corresponding to increasing levels of metabolic efficacy of a generic therapy. Samples of 1,000 virtual subjects each were simulated. For each subject in each sample, a lifestyle-like therapy (in terms of rapidity of onset and decay of effect) was started at the attainment of 7 mM glycemia. The 1,000 samples explored a range of peak efficacy of the therapy in modifying insulin sensitivity.

**Variable response to therapy.** The original DPP publications report a seemingly paradoxical phenomenon, an apparent discrepancy between initially dropping average glycemias vs. steadily increasing cumulative diabetes incidence (compare Figs. 2 and 3). One hypothesis to explain this phenomenon is to assume a variable impact of therapy over the studied patient sample, where those subjects who respond well drop their glycemia substantially, thus determining a therapy (i.e., the parameters representing rate of onset and rate of loss of efficacy of therapy over time) distributed asymmetrically around the corresponding projected means, allowing a substantial tail loss of efficacy of therapy over time) distributed asymmetrically to therapy (i.e., the parameters representing rate of onset and rate of loss of efficacy of therapy over time) distributed asymmetrically around the corresponding projected means, allowing a substantial tail.

**RESULTS**

Table 1 reports comparatively the age at enrollment and baseline glycemias of the observed and simulated samples for all four arms. The generating mechanism of the virtual patient population could match well the DPP cohort with respect to these parameters. The “percent enrolled” number represents the percentage of generated virtual subjects (arriving at enrollment) that were actually eligible for inclusion in the study. Figure 1 shows the actual distribution of enrollment glycemias from DPP superimposed on the distribution of enrollment glycemias required for the virtual sample to be accepted.

Figures 2 and 3 compare simulation results with observations for fasting glycemias and cumulative diabetes incidence, respectively. As can be seen, DPM reproduced, with good fidelity, the change in fasting glycemias observed in each of the four intervention groups of DPP. Likewise, simulated cumulative incidence of diabetes in each group is in good agreement with rates calculated from DPP based on FPG > 7 mM. In Fig. 3, the incidence of confirmed T2DM in DPP is also included, diagnosed on the basis of either FPG > 7 mM or G2h > 11.1 mM. Here, a difference exists between the steadily varying incidence of diabetes predicted by the model and the “saw-toothed” time course of incidence apparent in the DPP series (particularly for the lifestyle and metformin arms). In fact, in DPP, increases in incidence at full yearly intervals are larger because of diagnoses based on both fasting glycemias and OGTTs. Conversely, at midyear checks, only those subjects who had developed fasting hyperglycemia were diagnosable as diabetics, since OGTT was not performed during these visits. Also, the DPP-reported incidence of diabetes is generally higher than either the DPM-simulated incidence or the DPP data set-derived incidence of FPG > 7 mM.

Figure 4 shows the time course of hypothesized effects of the four treatments on insulin sensitivity. These effects are expressed as the mean percent change relative to the model-predicted value for that cohort of virtual subjects in the absence of intervention. The computed maximum mean improvement in insulin sensitivity is +3.5% for placebo, +45% for lifestyle, and +49% for troglitazone. The stipulated effect of metformin on insulin sensitivity results from the addition of fast (maximum effect +30%) and slow (maximum effect +15%) components required to replicate the changes in fasting glycemias and diabetes incidence among DPP subjects receiving this therapy.

Figure 5 depicts the predicted cumulative diabetes incidence rates based on peak insulin sensitivity improvements from 0 to +60%. Two hundred simulations are represented, with each point corresponding to a separate study conducted on 1,000 enrolled virtual subjects. The time course of the establishment...
and waning of the effect of therapy was assumed to be equal to that stipulated for the lifestyle treatment arm. Keeping other model parameters constant, these simulations predict a progressive reduction in diabetes incidence with greater increases in insulin sensitivity over this range. This relationship holds at 1, 2, and 4 yr of treatment, although cumulative diabetes incidence rates continue to rise. The shaded bands correspond to the maximal effects attributed in the present work to the placebo, lifestyle, and metformin regimens. As far as the present simulation study can assess, given the limitations in observation period, the effect of troglitazone was very similar to that of lifestyle. The wide scatter at 4 yr depends on the relatively small number of subjects attaining this length of study.

To further support the robustness of the model, its predictions have also been compared with the data published by Retnakaran et al. (30) relative the Canadian Normoglycemia Outcomes Evaluation (CANOE) study (also see Fig. 6, A and B, in the present work). In this case, it has been necessary to change the model’s parameters to reflect differences in average disease stage and average rapidity of evolution between the patient samples enrolled in the DPP and the CANOE studies. Thus, time to 50% normal insulin sensitivity changed from 1100 (DPP) to 1130 (CANOE) months prior to enrollment (taking as representative of the CANOE study a subject entering the study at 50 yr or 600 mo of age, hence 470 mo at 50% decay of insulin sensitivity), whereas the corresponding index changed from 18...
(DPP) to 8 (CANOE); these differences are consistent with a somewhat later but eventually faster development of insulin resistance in the DPP population.

The main difference between the two studies consisted of greater improvements in insulin sensitivity in the placebo group, which were apparently more intense and more prolonged in the CANOE study than in the DPP (+20% peak vs. +3.5% peak), which may reflect more intensive lifestyle counseling in the former study (41) and a correspondingly higher apparent effect of the composite active arm in CANOE vs. the separate effects in DPP (+80% peak metformin + rosiglitazone vs. +48% peak for TZD or +45% total for metformin). It is to be noted that whereas the model works with the K_gl index of insulin sensitivity (comparable with the intravenous glucose tolerance test’s SI in meaning and numerical values), the CANOE trial used Matsuda’s index, and proportional conversion of the first into the second was necessary to compare the predicted time course with the observed points.

It is common wisdom in clinical diabetology that oral hypoglycemic agents and moderate lifestyle changes, while being effective in the short to medium term (a few years), fail to prevent the eventual progression of the disease. Also, one of the recurring problems in diabetes research is the difficulty of obtaining long-term data series, following subjects over decades. Therefore, having demonstrated that DPM reproduced the progressive change in glycemia and the effects of interventions actually tested in the DPP study, it seems of interest to use the model to explore predicted effects of these and other more radical interventions on a much longer time scale. Figure 7 shows (for glycemia, β-cell mass, and insulinemia) the long-term model predictions for a subject with relatively fast and severe development of insulin resistance. In each graph, five curves are depicted, representing untreated progression of disease; conventional intervention on insulin sensitivity, similar to the DPP-intensive lifestyle modification both in intensity (increase by 50% over current levels) and in time course (peaking in 1–2 yr and then progressively abating); a similar improvement (50% over current levels, with same time course) in β-cell insulin secretory ability; a radical maneuver permanently preserving ≥10% normal insulin sensitivity for all time (i.e., allowing insulin sensitivity to decline to ≥10% of the “normal” 1 × 10^{-4} min^{-1} pM^{-1}), which is consistent with what is observed after bariatric surgery in morbidly obese diabetic patients (3, 27, 37, 38); and finally, a hypothetical effect on underlying islet inflammation, permanently decreasing by 20% the effects of glucose toxicity on β-cell replication. From the figures, a lasting effect on glycemic control can be attributed to bariatric and anti-inflammation therapy, whereas conventional approaches to increasing insulin sensitivity or β-cell insulin secretory capacity only determine a delay in the eventual development of markers of disease progression.

In order explore the consequences of the assumption that change in insulin sensitivity is the driver of glycemia and the underlying risk factor for developing diabetes, two more sets of simulations were performed, hypothesizing an isolated defect.
in insulin secretion (Fig. 8) or a combined defect in sensitivity and secretion (Fig. 9).

In the context of an original defect in insulin sensitivity, it can be appreciated from Fig. 7 that, although the evolution of insulinemia is of course very different if we intervene (with comparable intensity, i.e., by acutely increasing either insulin sensitivity or insulin secretory ability by 50% of the current value) on insulin secretory capacity rather than on insulin sensitivity, the corresponding evolution of glycemia is essentially identical (superposition of thick dashed gray and thin continuous black curves; Fig. 7), as is β-cell mass (given the same replication environment and the same glycemic stimulus/toxicity). In the case of an original isolated secretory defect (Fig. 8), the responses to conventional or dramatic increases in insulin sensitivity are in fact very similar (and rather ineffective), whereas a restoration of β-cell-replicating ability produces gradual, complete normalization of glycemia; interestingly, even a short-term (1 or 2 yr) conventional restoration of insulin secretion (e.g., by sulfonylureas) may produce a sufficient short-term drop of glycemia to reverse glucose toxicity and substantially alter the time course of the disease, with eventual increase of glycemia into diabetic territory delayed by decades. When considering coupled defects of similar intensity in both insulin sensitivity and secretion (Fig. 9), response to (even conventional) maneuvers enhancing secretion seems to be more favorable than response to maneuvers enhancing insulin sensitivity (even drastic ones like bariatric surgery); as in the previous case, restoration of β-cell-replicating ability is the only simulated maneuver apparently able to gradually reduce glycemia to normal levels.

In short, long-range simulations predict that in every case restoration of β-cell replication is successful in long-term reduction of glycemia, that drastic restoration of insulin sensitivity would work for primary insulin sensitivity defects, and that in the presence of significant components of original secretory ability defects even measures with temporary action on secretion may have long-lasting positive impacts on glycemia.

**DISCUSSION**

In the present work, the previously described DPM model (8) has been used to simulate the course of average glycemia and diabetes incidence in the four arms of the DPP study (19, 20). The adopted simulation algorithm produced a sample of subjects for each study arm whose glycemia and age distribution at enrollment matched the corresponding DPP group and whose rate of increase in glycemia varied depending on each subject’s past history and on the effectiveness of the applied treatment upon enrollment.

**Adherence of simulations to observations.** The reported results are the outcome of simulations of virtual subject samples, similar in size to the real observed samples. In adapting the model to the reported results from the DPP publications, there was some difficulty in matching the observed diabetes incidence rates. This was apparently due to several reasons, such as a difference in definitions (simulations being based on FPG, reported results on FPG and G2h), variation of the entry criteria for glycemia during the execution of the DPP study, and the requirement for confirmatory repeat testing in DPP, whereas in our simulations diagnoses are established by simply exceeding preallocated thresholds (7 mM FPG) at any single observation. We therefore recalculated diabetes incidence in the DPP data set using only the FPG threshold to allow a direct comparison with DPM simulations. We also excluded 59 subjects whose enrollment fasting glycemia exceeded 7 mM.

It must be underscored that, with the exception of insulin sensitivity, the many model parameter values employed for the simulation are identical for the four treatment arms and were derived from the previous in-depth literature search (8). In other words, structural parameter values of the glucose-insulin homeostatic control (with the exception of therapy-induced insulin sensitivity modifications) were not changed to specifically accommodate the DPP study results, which supports the robustness of the model. On the other hand, it was necessary to calibrate “driving” parameters, such as the distribution of rates of development of insulin resistance and the distribution of starting values of glycemia, to reflect the specific population under study. This was done...
in such a way as to match the distribution of age and entry
glycemia for simulation virtual subjects and real subjects. Once
matching distributions (the same for all treatment arms) were
obtained, the model ran its course for the subsequent length of
observation, with the sole difference in the time course of the
therapeutic effect on insulin sensitivity.

Given the above considerations, the model is shown to
replicate very well the results of the placebo, lifestyle, and
metformin arms of the DPP clinical trial, in particular repro-
ducing closely the observed cumulative incidence of FPG > 7
mM in years 1-4 of the study as well as the observed average
glycemias (Figs. 2 and 3).

It should be appreciated in this context that mere calibration
against DPP baseline glycemia distribution and against therapy-
specific diabetes incidence rates would not by itself assure con-
sistent reproducibility of observations by the model. The initial
drops in average glycemia in the context of continuing increase in
cumulative diabetes incidence, the simultaneous adherence to
both glycemias and incidence, the matching shape of predicted
curves and observations over time, and the consistency between
the postulated and literature-reported effect sizes of the different
therapeutic approaches could not all be attained by fitting the
model to the DPP data on a few free parameters unless the
intrinsic structure of the model was a plausible expression of
actual physiological mechanisms and unless key fixed parameters
were acceptably well approximated.

**Plausibility of the disease progression representation.** A few
considerations on the use of the current version of the DPM as
a support for clinical trial simulations are in order. The simu-
lation plan involved generating first a generic population of
virtual subjects by making the three parameters Gluc0, tI, and
νI vary to reproduce a distribution of different life histories
from the point of view of the rate and severity of development
of insulin resistance. The DPP study enrollment criteria and the
DPP observed distribution of ages were then applied to this
generic population to obtain a sample of virtual subjects. For
each study arm, the “enrolled” virtual subjects were then
followed for lengths of observation, again replicating the
observed distribution in the DPP study. The original distribu-
tions of Gluc0, tI, and νI were adapted so that, after the
application of enrollment criteria, the distribution of enroll-
ment glycemias and the rate of progression of disease matched
those found for the DPP cohorts. From this adaptation exercise,
it appears that the glucose-insulin homeostasis system is robust to substantial decrements of (isolated) insulin
sensitivity, glycemia derangements occurring only when
insulin sensitivity goes below 0.2 min⁻¹ pM⁻¹ for
lengthy periods. This is in fact consistent with what has been
observed in the Insulin Resistance Atherosclerosis Study (15),

![Graph A](http://example.com/graphA.png)

**Fig. 7.** Single-subject simulation for a subject with early severe (down to 5% normal) decrease of insulin sensitivity showing predicted time course of glycemia (A), β-cell mass (B), and insulinemia (C) in the natural, unmodified state (solid gray curve) and following 4 types of pharmacological intervention, each starting at the moment glycemia increases to > 7 mM: temporary increase of insulin sensitivity by 50% (dashed gray curve), temporary increase of β-cell secretory ability by 50% (thin black curve), radical maneuvers (hypothetically, bariatric surgery) maintaining insulin sensitivity at or > 10% normal thereafter (dotted curve), and radical maneuvers (hypothetically β-cell anti-inflammatory treatment) suppressing glucose toxicity by 20% long term (black dashed curve).
where subjects with average age of 57 yr and average insulin sensitivity around $0.35 \times 10^{-4} \text{min}^{-1} \text{pM}^{-1}$ constituted the normal glucose tolerance group and where IGT and T2DM groups had average insulin sensitivities of 0.181 and 0.079 min$^{-1}$pM$^{-1}$, respectively. Of course, DM can occur with lesser degrees of insulin resistance in the presence of a significant $\beta$-cell defect.

Assumed mechanism of therapies. A second consideration regarding the described simulation plan concerns the choice of the insulin sensitivity index $K_{xgI}$ as the primary site of action of the therapeutic regimens under investigation. This approach was felt to be justified based on the mechanisms of action described in the literature for the particular interventions used in DPP.

Regarding lifestyle modification, both cross-sectional and longitudinal studies have reported that physical activity and weight loss improve insulin sensitivity (12, 16, 24, 31, 33, 39). Improvement in insulin sensitivity is considered to be the primary mode of action for troglitazone and other thiazolidinediones, and these effects have been documented in a number of studies (2, 13, 18, 25). Metformin is thought to act primarily by reducing hepatic glucose production, but it is also believed to have an effect on insulin action, and several clamp studies suggest modest effects on insulin sensitivity (2, 10, 17, 35).

Other pharmacological effects, besides the action on insulin sensitivity, could well have been present, and these could in fact be expressed as changes in model parameters (e.g., the effect of thiazolidinedione compounds on insulin secretion could have been represented as an increase in the parameter expressing insulin secretory ability by existing $\beta$-cells). However, since the observed changes in glycemia and diabetes incidence could be predicted on the basis of modifications of $K_{xgI}$ alone, and since this action is undisputed and common to all treatment regimens investigated, parsimony considerations dictated to maintain the simplest possible simulation structure compatible with available data, and therefore, the sole effect on insulin sensitivity was considered.

Changes in insulin sensitivity and insulin secretion after 1 yr of intervention in the DPP study have been reported previously (20); consistent with the approach taken in our current study, the DPP investigators reported improvements in surrogate measurements of insulin sensitivity with troglitazone, metformin, and lifestyle interventions but no improvements in measurements of insulin secretion in any group. Although other studies have noted improvements in insulin secretion with similar interventions, it is not well established whether these represent direct or indirect effects on $\beta$-cell function. A structural feature of the present model is that temporary mitigation of insulin sensitivity does reflect positively on $\beta$-cell net

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**Fig. 8.** Single-subject simulation for a subject with early severe (down to 5% normal) decrease in insulin secretory capacity showing predicted time course of glycemia (A), $\beta$-cell mass (B), and insulinemia (C) in the natural, unmodified state (solid gray curve) and following 4 types of pharmacological intervention, each starting at the moment glycemia increases to $>7$ mM: temporary increase in insulin sensitivity by 50% (dashed gray curve), temporary increase in $\beta$-cell secretory ability by 50% (thin black curve), radical maneuvers (hypothetically, bariatric surgery) maintaining insulin sensitivity at or $>10\%$ normal thereafter (dotted curve), and radical maneuvers (hypothetically $\beta$-cell anti-inflammatory treatment) suppressing glucose toxicity by 20% long term (black dashed curve).
replicating ability and may therefore produce appreciable effects on insulin secretion.

Comparison of assessed and literature-derived effects of therapies on insulin sensitivity. Once the choice of focusing attention on the KxgI parameter was made, another point to be considered was whether the model was quantitatively compatible with commonly accepted sizes of the effects of the administered therapies. The maximum change in insulin sensitivity that made our simulations well adapted to the DPP data was +3% for placebo, +50% for lifestyle, +45% for metformin, and +49% for troglitazone. These values are modestly different from those reported by the DPP authors themselves (20): +9% for placebo, +29% for lifestyle, +24% for metformin, and +47% for troglitazone based on a surrogate parameter (1/fasting insulin). In this respect, it must be noted first of all that the available estimates of therapy effect on insulin sensitivity do not agree very precisely, possibly as a consequence of the different techniques that have been used in different publications to obtain these estimates. Thus, for metformin administration, an effect as low as +13% over baseline (17) or as high as +40% (10) has been reported; lifestyle effect varied between +21% (34) and +55% (33), whereas the thiazolidinedione effect has been reported to be as low as +38% (13) and as high as +67% (26). Effect sizes that we derived from model adaptation to observations in the DPP data set were within the range of these literature estimates.

In this respect, the effect size attributed to the troglitazone arm could be questionable. Troglitazone was retired from the market midway through the DPP study due to concerns of potential liver toxicity, with the result that observed diabetes incidence refers in any case to shorter observation times than the other arms, and could have been affected by patient withdrawal or continued observation under different therapy.

The therapeutic effect on insulin sensitivity was expressed as a percent increase with respect to theoretical or “natural” insulin sensitivity induced by the regimen at a given time point. In other words, for each virtual subject a numerical prediction of what would have been the natural, untreated time course of insulin sensitivity over the period of observation was first computed. This depended on such characteristics as age at entry, slope of decline of insulin sensitivity over the years, and time to reach 50% of basal insulin sensitivity. At each time point, this natural insulin sensitivity was then augmented by a variable percentage, reflecting the effectiveness of the treatment regimen at that time point. Treatment regimens were in fact not supposed to produce immediate maximum efficacy and maintain this maximum efficacy indefinitely (step increase) but rather increase progressively in efficacy, reach a maximum effect, and then regress progressively toward zero. Increase in efficacy could be made to be so fast as to

Fig. 9. Single-subject simulation for a subject with early moderate (down to 25% normal) decrease in both insulin sensitivity and insulin secretory capacity showing predicted time course of glycemia (A), β-cell mass (B), and insulinenia (C) in the natural, unmodified state (solid gray curve) and following 4 types of pharmacological intervention, each starting at the moment glycemia increases to >7 mM: temporary increase of insulin sensitivity by 50% (dashed gray curve), temporal increase in β-cell secretory ability by 50% (thin black curve), radical maneuvers (hypothetically, bariatric surgery) maintaining insulin sensitivity at or >10% normal thereafter (dotted curve), and radical maneuvers (hypothetically β-cell anti-inflammatory treatment) suppressing glucose toxicity by 20% long term (black dashed curve).

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be essentially immediate, whereas decrease in efficacy could be made to be so slow as to be equivalent to indefinite persistence of the effect while under treatment; therefore, under both of these conditions the step increase pattern of treatment effect was reproducible.

For the placebo, lifestyle, and troglitazone arms a single, homogeneous, increasing and then decreasing pattern of treatment efficacy was sufficient to reproduce with good approximation the observed fasting glycemias and incidence of FPG $>$ 7 mM. However, for metformin, this representation proved to be insufficient, and it was necessary to postulate the superposition of an immediately appearing effect (+15% at peak) coupled with the establishment of a slower effect (responsible for an additional +30% maximum). It is possible that this is a reflection of previously observed multimodal actions of metformin. For example, direct suppression of gluconeogenesis (10) or enhanced incretin secretion (7, 14, 22) could contribute to immediate effects, whereas slower effects could relate to improvement in peripheral insulin sensitivity. We believe these more complex drug mechanisms are tractable with DPM but may require adaptation of the model to explicitly represent these processes.

Adapting model predictions to observations has thus yielded estimates of the effect of the several regimens on insulin sensitivity, with the caveat that any such estimates are conditional on all other parameters remaining the same (and in fact assuming standardized values), which is certainly an oversimplification. However, keeping this caveat in mind, it can be appreciated that the treatment effects, assessed by adapting the model to the available observations, agree with the existing literature sources at least as closely as these sources agree among themselves. The advantage of using the model in these circumstances is that once a quantitative estimate of the effect of treatment is obtained from short-term observations, its long-term effects may be forecast. These need not be, and in general are not, naively proportional to the short-term gain, given the highly nonlinear interplay of the several factors concurring in determining glucose homeostasis. This can be well appreciated from Fig. 6, where the model predicts that long-term glycemia and insulinemia eventually follow the same time course (albeit somewhat delayed) in the presence or absence of what seems to be, in the short term, a highly effective regimen (such as DPP-intensive lifestyle modification). Over time, the natural progression of the disease effectively abrogates any short-term advantages of one regimen over the others. This is in fact consistent with clinical practice, where it is common to control glycemia and to administer progressively increasing dosages of eventually multiple agent combinations.

A major qualitative difference is obtained only when the fundamental mechanisms of the progression of disease are altered, for instance, guaranteeing maintenance of insulin sensitivity to a sizeable fraction of normal, as could be the case of drastic fat tissue loss after major metabolic surgery procedures.

Comparison with the results of the CANOE study. The model predictions appear to adapt well to the results of the CANOE study published by Retnakaran et al. (30), and the measurements of the effects correspond very well for both the placebo arms and the DPP metformin or rosiglitazone arms on the one hand and the CANOE metformin plus rosiglitazone arm on the other. It must be underscored that transformation of the $K_{sdt}$ index of insulin sensitivity into the Matsuda index was made extemporarily and that the fit in this case essentially concerns the relative time course, whereas absolute values are arbitrary. In fact, the underlying primary defect was taken to be an isolated defect in insulin sensitivity for the CANOE study as well, without any impairment of insulin secretory ability. If a concurrent primary defect in insulin secretion was taken to be present, the $K_{sdt}$ decrement needed to reproduce the observed glycemias would be less important, and although the graphs in Fig. 6 would still appear to be very similar, a different conversion coefficient between $K_{sdt}$ and Matsuda indices would be used.

Long-term predictions based upon model. Supposing the model to be reliable, within the evident limits of such a schematic representation of reality, it is of immediate interest to use it to answer some basic questions about disease evolution and effectiveness of therapy. It has to be kept in mind that when the model is left to run freely for several years in the life history of a virtual patient, state variables may assume values that in real life would be prevented by the administration of therapy. This applies particularly to glycemia, which the model may predict to increase to more than 20 mM, although in reality the subject would come to medical attention well before these levels are reached. In turn, such persistent high glycemias negatively affect $\beta$-cell population (given the glucose toxicity mechanism incorporated in the model) until potential disappearance of insulin secretion. Therefore, keeping in mind that the model depicts theoretical, unrestrained evolutions, it has been discussed above how limited-impact pharmacological or lifestyle interventions (directed to improving either insulin sensitivity or insulin secretion), occurring at the moment of clinical evidence of the consequences of long years of progressive homeostatic derangement, may offer modest and temporary slowing in the progression of the disease and that conversely the long-term maintenance of even a modest fraction of the normal levels of insulin sensitivity, or the suppression of a fraction of the inflammation-mediated glucose toxicity, could substantially alter the evolution of the clinical picture. $\beta$-Cell mass is predicted by the model to eventually disappear if glycemia is left to soar uncontrolled. It is conversely maintained if a new equilibrium at modest but nonvanishing insulin sensitivity is reached with compensating hyperinsulinemia and modest, nondiabetic increase in glycemia. In this sense, the model supports the use of early preventive measures directed at limiting the occurrence of the dangerous positive feedback loop of high glycemia, glucose toxicity, diminished pancreatic reserve, and still higher glycemia.

Lack of separate central and peripheral insulin actions. A potential problem with the modeling approach followed so far concerns the lack, at the present stage, of independent characterization of fasting vs. 2-h glycemia, as a consequence of the lack of separate central and peripheral insulin actions in the model (FPG being more closely dependent on central and G2h more dependent on peripheral insulin sensitivity), so that the model does not currently discriminate between IFG and IGT in the progression toward T2DM.

Another limitation of the current model is the lack of a renal glucose elimination term. Renal glucose elimination takes place at glycemia levels greater than some concentration thresholds (in the neighborhood of 10 mM), which is in any case substantially larger than the diabetes diagnosis threshold of 7 mM considered in the present work. Therefore, for all practical purposes the current model performs correctly until glycemia exceeds the renal glucose elimination threshold, correctly portrays the subject’s evolution at least until the
diagnosis of diabetes, and thus correctly accounts for the incidence of FPG >7 mM. However, this limitation will also have to be addressed in future work.

Further work directed at refining and further validating the model will have to address the incorporation of renal glucose excretion, the incorporation of both central and peripheral mechanisms of insulin sensitivity (hence, consideration of the impact of both fasting and postprandial glycemia), possible refinement of parameters related to β-cell turnover and β-cell mass as new data become available, and possible validation against other large data sets.

Conclusion. The previously proposed DPM structural physiological model for the progression of diabetes has been shown to closely match an actual series of clinical observations from the DPP study. The model’s parameters have a direct pathophysiological meaning and may be varied to reflect drug action in subgroups. The DPP study results have been replicated by assuming a single general form of the model as well as common parameter values, varying between treatments the single parameter expressing the average increase in insulin sensitivity, achieved with the treatment over the study period.

The results obtained so far indicate that the DPM predicts important diabetes progression end points with good fidelity, and the current results provide further support for the validity and utility of this physiology-based model. Of particular interest, we believe that DPM has potential for being used for in silico evaluation and clinical trial design for novel and existing therapies; physiologically based clinical trial simulation in T2DM can help forecast the results of clinical studies based on established biological effects. Although certainly still a work in progress, the present attempt at a carefully constructed and motivated model for long-term diabetes development may provide a hitherto missing tool for the study of diabetes progression and could be of practical utility to all interested parties.

DISCLOSURES

Thomas Hardy, Eyas Abu-Raddad, and Niels Porksen are employees of and hold stock in Eli Lilly and Company. Eli Lilly manufactures and sells pharmaceutical treatments for diabetes mellitus. The present work is relevant to diabetes therapies, although no Eli Lilly products are discussed. A. De Gaetano is an employee of CNR IASI “A. Ruberti”, which received payment from Eli Lilly for work leading to the results described in this article.

AUTHOR CONTRIBUTIONS

T.H., E.A.-R., N.P., and A.D.G. did the conception and design of the research; T.H. and A.D.G. analyzed the data; T.H., E.A.-R., N.P., and A.D.G. interpreted the results of the experiments; T.H. and A.D.G. drafted the manuscript; T.H., E.A.-R., N.P., and A.D.G. edited and revised the manuscript; T.H., E.A.-R., N.P., and A.D.G. approved the final version of the manuscript; A.D.G. performed the experiments; A.D.G. prepared the figures.

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