A Mechanistic Disease Progression Model for Type 2 Diabetes Mellitus and Pioglitazone Treatment Effects

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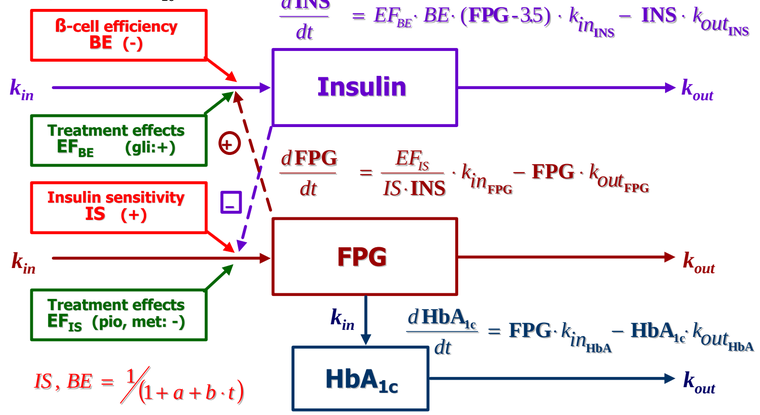
Introduction

Type 2 Diabetes Mellitus (T2DM) is characterized by the progressive failure of pancreatic *b*-cells to compensate declining insulin sensitivity with increased insulin secretion. Traditional treatment options tend to provide short-term relief but typically fail to prevent the relentless progression of T2DM, which continues over many years (UKPDS 33 and 34). Because clinical trials of antidiabetic agents are usually restricted to timescales of weeks or months, novel tools are needed to extrapolate the results of such relatively short-term clinical trials over the longer term of T2DM progression. In previous studies we developed a cascading model for T2DM disease progression in which change in fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1c}) was modeled as a cascading sequence, and disease progression was described as a time dependent, saturable process that was counter-acted by treatment. It indicated that pioglitazone prevents the progression of T2DM. Here we extend the model cascade with the homeostatic feedback relationship between fasting plasma glucose and insulin (Matthews et al.1985). This resulted in a mechanistic model for T2DM disease progression that was used to compare the long-term effects of pioglitazone, metformin and gliclazide on *b*-cell efficiency and insulin sensitivity in a random subset of 400 newly diagnosed T2DM patients.

Model Structure: FPG-Insulin Homeostasis

The core of the mechanistic model consists of the homeostatic feedback between FPG and insulin for glycemic control as described in Matthews et al. (1985), integrated with the previously developed FPG-HbA_{1c} cascade:



$$\frac{d\,INS}{dt} = EF_{BE} \cdot BE \cdot (FPG - 3.5) \cdot k_{in_{INS}} - INS \cdot k_{out_{INS}}$$

$$\frac{d\,FPG}{dt} = \frac{EF_{IS}}{IS \cdot INS} \cdot k_{in_{FPG}} - FPG \cdot k_{out_{FPG}}$$

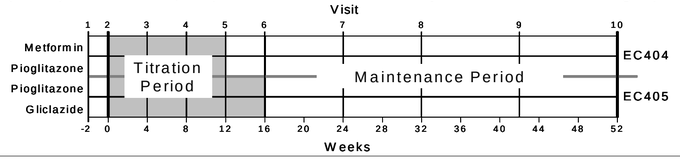
$$\frac{d\,HbA_{1c}}{dt} = FPG \cdot k_{in_{HbA}} - HbA_{1c} \cdot k_{out_{HbA}}$$

$$IS, BE = \frac{1}{1 + a + b \cdot t}$$

In the above model, rising FPG levels stimulate the production of insulin in the *b*-cells, which, in turn, suppresses the production of glucose in the liver and hence brings FPG down again. When insulin sensitivity in the liver (IS) decreases, increased insulin secretion is required to bring FPG levels down and maintain glycemic control. However, if *b*-cell efficiency (BE) also decreases, at some point insulin secretion will no longer be able to compensate for the decreased insulin sensitivity, FPG levels will go up, and diabetes will ensue. In order to capture the progressive nature of T2DM both IS and BE were modeled as asymptotically decreasing functions of time. The treatment effect of gliclazide, as an insulin secretagogue, was modeled as a step-function increasing insulin production, thus counteracting decline in BE. Pioglitazone and metformin are both insulin sensitizers, and their efficacies were modeled as step-functions increasing the suppressing effect of insulin on glucose production, thus counteracting decline in IS (EF_{IS}). Typical FPG and fasting insulin levels for healthy subjects as estimated by Matthews et.al (1985) were substituted in the differential equations above, yielding steady-state equations for *BE* and *IS* identical to the tried and tested HOMA formulae for *ß*-cell function and insulin sensitivity. This means that the model can express T2DM disease progression in terms of changing HOMA estimates for *ß*-cell function and insulin sensitivity over time. Moreover, it allows the estimation of disease status for each patient at baseline.

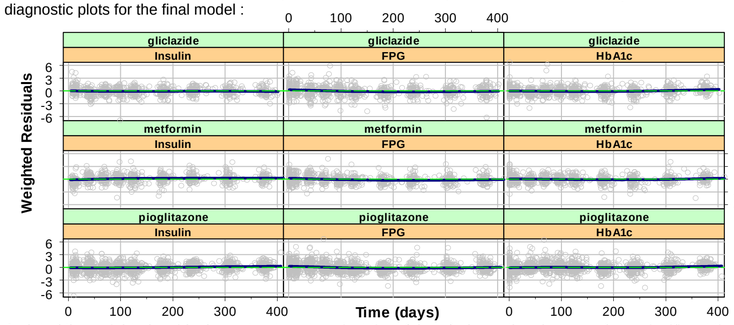
Materials and methods

The mechanistic T2DM disease progression model was implemented as a population pharmacodynamic model in NONMEM V.1., and optimized on two Phase III, one-year efficacy studies comparing pioglitazone to metformin or sulphonylurea in mono-therapy in a random subset of 400 from a total of 2408 newly diagnosed T2DM patients. Both studies were multicenter, randomised, double-blind, double-dummy, parallel-group studies on the long-term safety and efficacy of pioglitazone *versus* metformin (EC404) or gliclazide (EC405) for the treatment of T2DM in male or female type 2 diabetes mellitus patients inadequately controlled by diet alone. Glycemic control was evaluated with change in HbA_{1c} (%) as the primary efficacy parameter; fasting plasma glucose (FPG) and fasting insulin were measured as secondary efficacy parameters. The study duration of 52 weeks was preceded by a 2-week screening period, and consisted of a 12-week forced titration period followed by a 40-week maintenance period at the individual optimal dose (EC404) or a 16-week titration period followed by a 36-week maintenance period (EC405). Baseline levels, compliance and withdrawal were very similar between treatment groups.

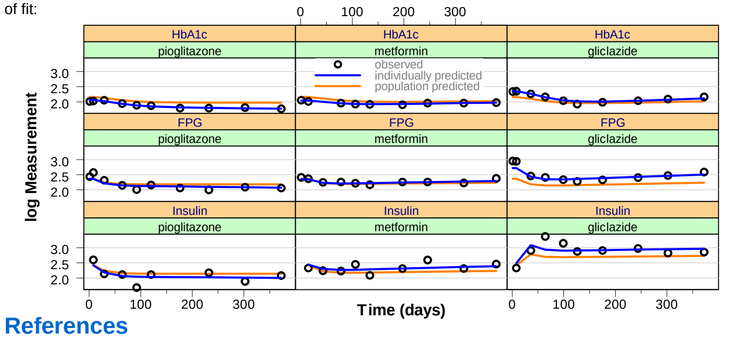


Model Diagnostics

The principle of parsimony was applied to the model development, such that the simplest model that described the data adequately was selected as the final model. The influence on the model fit of adding an additional model parameter (either structural or stochastical) to the model was analyzed according to the usual graphical and statistical diagnostic criteria (Boeckmann, Sheiner and Beal 1994; Pinheiro and Bates 2000). See below for some diagnostic plots for the final model :



A plot of the weighted residuals per treatment against time (above) shows the absence of any significant time-dependent bias in the model fit. Below, some typical individual model fits further illustrate a satisfactory goodness of fit:



References

AJ Boeckmann, LB Sheiner and SL Beal (1994). NONMEM Users Guide – Part V. San Francisco: NONMEM Project Group.
DR Matthews, JP Hosker, AS Rudenski, BA Naylor and RC Turner. Homeostasis model assessment: insulin resistance and *ß*-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985: 412-419.
Pinheiro, J.C. and Bates, D.M. (2000). *Mixed-Effects Models in S and S-PLUS.* New York: Springer.
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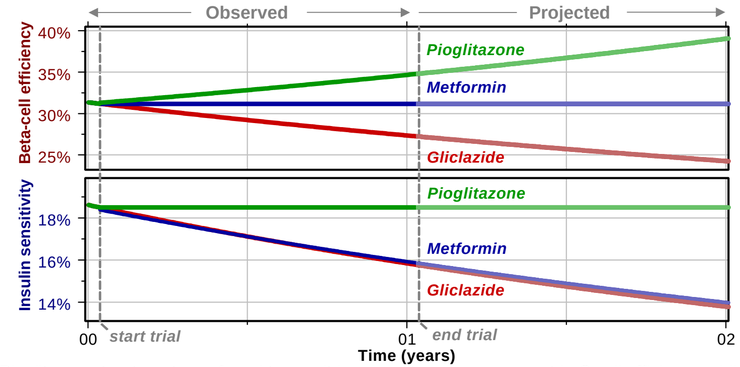
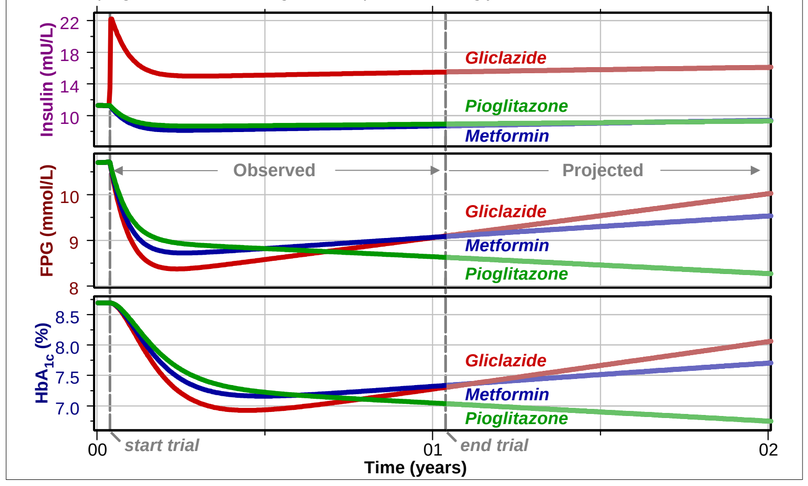
Model Results

The figure below shows the long-term effects of the various treatments on T2DM disease progression, combined with the extrapolated model predictions for a second year of treatment.



Pioglitazone treatment was found to result in a long-term improvement in ß-cell efficiency while keeping insulin sensitivity stable for the entire duration of the trial. In contrast, metformin showed continuing disease progression in insulin sensitivity while keeping ß-cell function stable, and gliclazide showed a continuing decline in both insulin sensitivity and ß-cell efficiency. Hence, both gliclazide and metformin showed a continuing deterioration of glycemic control with time, whereas pioglitazone showed a gradual improvement of glycemic control with time:



Conclusions

- **The incorporation of the glucose-insulin homeostasis into the model cascade allows a mechanistic representation of T2DM disease progression, which can be expressed in change in *ß*-cell function and insulin sensitivity over time.**
- **This mechanistic model can be used to extrapolate inherently short-term clinical trials to predict the long-term effects of treatment on T2DM progression.**
- **The model results suggest that pioglitazone protects against T2DM progression and may even reverse disease progression by gradually enhancing *ß*-cell efficiency, thus continuing to improve glycemic control over the longer term.**