Type 2 Diabetes Mellitus (T2DM) is characterized by the progressive failure of pancreatic β-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 timetables 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 (HbA1c) was modeled as a cascading sequence, and disease progression was described as a time dependent, saturable process that was counteracted 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 β-cell efficiency and insulin sensitivity in a random subset of 400 newly diagnosed T2DM patients.

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-HbA1c cascade:

\[ \frac{dFPG}{dt} = \frac{E_F}{IE_F} \cdot (FPG - FPG_{35}) - k_{out} \cdot FPG \]

\[ \frac{dHbA1c}{dt} = \frac{E_H}{IE_H} \cdot (HbA1c - HbA1c_{min}) - k_{out} \cdot HbA1c \]

In the above model, rising FPG levels stimulate the production of insulin in the β-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 β-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 countering effect of 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 countering decrease in IS (E_I).

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.

References


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 β-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. The model results suggest that pioglitazone protects against T2DM progression and may even reverse disease progression by gradually enhancing β-cell efficiency, thus continuing to improve glycemic control over the longer term.