The variability in beta-cell function in placebo-treated subjects with type 2 diabetes: Application of the Weight-HbA1c-Insulin-Glucose (WHIG) Model

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ABSTRACT

Aim: The Weight-HbA1C-insulin-glucose (WHIG) model described the change in weight on insulin sensitivity (IS) in newly-diagnosed, obese subjects receiving placebo treatment. This model was applied to a wider population of placebo-treated subjects to investigate factors influencing the variability in IS and β-cell function.

Methods: The WHIG model was applied to the WHIG dataset (Study 1) and two other placebo datasets (Studies 2 and 3). Studies 2 and 3 consisted of non-obese subjects and subjects with advanced T2DM. Body weight, fasting serum insulin (FSI), fasting plasma glucose (FPG) and HbA1c were used for non-linear mixed effects modelling (software, NONMEM v7.2). Sources of inter-study variability (ISV) and potential covariates (age, sex, diabetes duration, ethnicity, compliance) were investigated.

Results: An ISV parameter for baseline parameters (body weight and β-cell function) was required. The baseline β-cell function was significantly lower in subjects with advanced T2DM (Study 2: median difference, 15.6%, $P<0.001$; Study 3: 22.7%, $P<0.001$) than subjects with newly-diagnosed T2DM (Study 1). A reduction in the estimated insulin-secretory response in subjects with advanced T2DM was observed but diabetes duration was not a significant covariate.

Conclusion: The WHIG model can be used to describe the changes in weight, IS and β-cell function in the diabetic population. IS remained relatively stable between subjects, however large inter-subject variability in the β-cell function was observed. There was a trend towards decreasing β-cell responsiveness with diabetes duration, and further studies incorporating subjects with a longer history of diabetes is required.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Type 2 diabetes mellitus (T2DM) has a very slow disease progression, which is associated with the gradual decline in β-cell function.
- The Weight-HbA1c-Insulin Glucose (WHIG) model described the effects of placebo treatment on β-cell function and insulin sensitivity in newly-diagnosed, obese subjects with T2DM
- It is not known whether the WHIG model can be applied to a wider population of people with T2DM.

WHAT THIS STUDY ADDS

- The WHIG model described the disease progression of T2DM in a wider population of subjects with T2DM including subjects with advanced T2DM.
- The variability in the insulin sensitivity was small, but there was large inter-individual variability in β-cell function.
- Diabetes duration was not a significant covariate for the β-cell parameters but a trend towards lower β-cell function with diabetes duration was observed.

TABLE OF LINKS

LIGANDS
Insulin

This Table of Links list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e] Alexander et al., 2015a,b,c,d,e).

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycaemia due to insulin resistance and pancreatic β-cell dysfunction. If T2DM is left untreated, people with T2DM are at risk of developing many microvascular and macrovascular complications [1]. However, it is the continued deterioration in β-cell function that undermines the long-term effectiveness of many antidiabetic drugs to maintain euglycemia [2]. Therefore, it is not surprising that the goal in the treatment of T2DM has shifted from maintaining euglycaemia to delaying the progression of the disease by restoring or slowing the decline in β-cell function [3, 4].

The function of pancreatic β-cells cannot be measured directly and methods to assess the changes in β-cell function are required. The pancreatic β-cells respond to high glucose concentrations by increasing the release of insulin from the pancreas. Therefore, the concentrations of fasting serum insulin (FSI) and fasting plasma glucose (FPG) can be used to reflect the balance between hepatic glucose output and insulin secretion, maintained by a feedback loop between the liver and the β-cells [5]. This relationship can be described mathematically using the model of homeostasis (HOMA) to estimate the β-cell function and insulin sensitivity in people with T2DM [5, 6].

There are two semi-mechanistic models that had utilized the homeostatic relationship between FSI and FPG. The de Winter model [7] was first developed to describe the progression of T2DM in subjects treated with either metformin, gliclazide or pioglitazone. Glycosylated haemoglobin (HbA1c), a marker of glucose exposure over 3 months, was also described in the model using a feed-forward mechanism between FPG and HbA1c. This model was recently updated to the Weight-HbA1c-Insulin-Glucose (WHIG) model to include the effect of weight on insulin sensitivity in placebo-treated subjects [8, 9]. In this study, the change in body weight was found to be a driver of insulin sensitivity, whereby a median

weight loss of 4.1 kg was associated with a 30% increase in insulin sensitivity [8]. Furthermore, the HbA1c model was expanded to include three transit compartments, to reflect the lifespan of the glycated red blood cells [8].

The WHIG model has only been evaluated in newly-diagnosed, obese subjects who entered a weight loss program. These subjects only represent a subset of the entire diabetic population and it is not known whether this model can be used to describe the changes in weight, insulin sensitivity and β-cell function in the wider diabetic population. Therefore, the aim of this study was to investigate the use of the WHIG model in a wider population of placebo-treated subjects with T2DM and to examine factors that may influence the variability in the parameter estimates.

METHODS

Datasets

Data from placebo arms of 3 clinical trials in patients with T2DM were used in this study, including the dataset used to build the WHIG model (Study 1, [8]). The data was obtained from placebo arms of randomized, double blind, multi-centre, placebo-controlled Phase 2/3 clinical trials. The study design of the placebo arms are described in Table 1. Study 1 included a weight loss component, whilst subjects from Studies 2 and 3 were maintained on a stable diet and exercise regimen. The study was conducted according to International Conference on Harmonization Good Clinical Practice guidelines, and applicable laws and regulations. Ethics approval was obtained from the institutional review board and informed written consent was obtained from each subject. The ClinicalTrials.gov identifier for these studies are NCT0023660 (Study 1), NCT01071850 (Study 2) and NCT01117584 (Study 3).

Study 1 (n = 181) included newly diagnosed, treatment naïve, obese subjects (BMI >27 kg/m^2 and <50 kg/m^2) to investigate the effect of diet and exercise on weight loss and glucose control. Subjects first entered a 6-week placebo run-in before the placebo treatment phase (placebo treatment). These subjects were followed for up to a total of 66 weeks.

Study 2 consisted of treatment naïve subjects (n = 29) and subjects who were previously treated with an antidiabetic drug (n = 37). Subjects who were previously treated, entered a 6-week washout phase, followed by a placebo run-in phase (2 weeks) and placebo treatment phase (12 weeks). Treatment naïve subjects only entered the placebo run-in phase and placebo treatment phase.

Study 3 (n = 65) included subjects who were inadequately controlled on metformin (1500 mg daily, HbA1c >7%) for at least 6 weeks prior to the start of the study. In contrast to Study 2, these subjects did not enter a washout phase prior to the start of the study. This study also consisted of a 2-week placebo run-in followed by a 12-week placebo treatment phase (placebo treatment).

Measurements of Weight, FSI, FPG and HbA1c

The timing and frequency of weight measurements and the collection of FSI, FPG and HbA1c samples are shown in Supplementary Table S1 and Supplementary Table S2. In all studies, weight was measured at every clinic visit. For Study 1, up to 22 weight measurements were recorded, whilst Studies 2 and 3 had 7 measurements of weight from each subject.

FSI was measured less frequently than the other glycemic markers. In Study 1, there were up to 4 observations of FSI for each subject. Similarly, 5 observations of FSI were recorded from each subject in Studies 2 and 3. In Study 1, there were 18 measurements of FPG and 19 measurements of HbA1c from each subject. In Studies 2 and 3, there were 7 FPG observations and 6 HbA1c measurements from each patient. Subjects were previously treated with antidiabetic drugs in Study 2, entered a 6-week washout phase prior to the start of the study. These subjects had an additional measurement of weight, FSI, FPG and HbA1c at 6 weeks prior to the start of the study.

The WHIG model

The WHIG model [8] is shown in Supplementary Figure 1. This model consisted of a turnover model for body weight, a closed form solution for FSI and FPG with steady-state assumptions, and three transit compartments for HbA1c [8]. The equations relevant to this study (treatment effects, insulin sensitivity and β-cell function) are outlined below. The glucose-insulin homeostasis was modelled as a feedback mechanism between FSI and FPG and these equations are shown in Supplementary (NONMEM control stream).

Dynamics of body weight

A turnover model was used to describe the dynamics of body weight (Supplementary Figure S1). The effects of diet and exercise counselling and placebo treatment on body weight were modelled as two step-functions: a treatment effect of diet and exercise counselling at screening ($EF_{DE}, t > 0$) and a placebo treatment effect at the start of placebo treatment phase (EF_{PL}, $t >$ placebo run-in phase). EF_{DE} and EF_{PL} were expressed as a relative change from

baseline. The treatment effects of placebo, diet and exercise, however, can wear off with time. A linear rate of loss function (EF_{LOSS}) was added to describe the wearing off of treatment effects with time (Eq. 1). The net treatment effect on body weight (EF_W, Eq. 1) was modelled on the input side of the turnover model of body weight (Eq. 2).

$$EF_W = \frac{(100 - (EF_{DE} + EF_{PL}))}{100} \times \frac{(100 + (EF_{LOSS} \times {}^{t}/_{365}))}{100}$$

Eq. 1

$${}^{dWGT}/_{dt} = WGT_{kin} \times EF_W - WGT_{kout} \times WGT$$

Eq. 2

where *t* is time in days.

Insulin sensitivity (IS)

The dynamics of insulin sensitivity (IS) is driven proportionally by the change in body weight (ΔWGT). The effect of weight change on insulin sensitivity (EF_S, Eq. 3) was scaled with a scaling factor ($Scale_{EFS}$):

$$EF_S = 1 + Scale_{EFs} \times \Delta WGT$$

Eq. 3

ΔWGT was calculated as the difference between the baseline weight and the current weight. At baseline ($t = 0$), the value of EF_S is 1. A reduction in weight from baseline will increase insulin sensitivity (EF_S >0), while an increase in weight will result in a decrease in insulin sensitivity (EF_S <0).

The *IS* was then calculated using the estimated baseline insulin sensitivity as a logit function (s_0):

$$IS = \frac{1}{1+ exp^{(s_0)}} \times EF_S \quad \text{Eq. 4}$$

Dynamics of β*-cell function*

The dynamics of β-cell function was modelled as the result of two components: a disease progression component (*BF*) and a treatment effect (EF_B). *BF* is a logistic decay function to describe the natural deterioration in β-cell function from baseline (Eq. 5). It consists of parameters to estimate the baseline β-cell function (b_0) and the rate of β-cell decline per year from baseline (r_B):

$$BF = \frac{1}{\left(1+ exp^{(b_0+ r_B \times t/365)}\right)} \quad \text{Eq. 5}$$

where *t* is time in days. b_0, like $s_{0,}$ provides an indicator of the disease status of subjects at study entry. The parameter r_B can have either a positive or negative value to indicate either a decline in β-cell function with time, or an improvement in β-cell function over time.

In the WHIG model, the treatment effect, EF_B, was estimated empirically and was modelled with a logistic increase and decline to describe the initial improvement and subsequent decline in the β-cell function due to the effect of weight loss [8]. Since Studies 2 and 3 were short trials, this treatment effect was simplified to a step function (Eq. 6):

$$EF_B = 1 + EF_{BT} \times OC_1 \quad \text{Eq. 6}$$

where EF_{BT} is the estimated treatment effect and OC_1 is a parameter to switch on the treatment effect. At baseline (t = 0), $OC_1 = 0$ to indicate no treatment effect ($EF_B = 1$). At $t > 0$, OC_1 takes the value of 1 to switch on the effect of placebo treatment on the β-cell function.

A limitation of using the step function is that the treatment effect remains constant throughout the duration of the study and changes in the treatment effect with time cannot be described. The overall effect of β-cell function on FSI production is a function of BF and EF_B (Eq. 7):

$$B = BF \times EF_B \quad \text{Eq. 7}$$

Dynamics of HbA1c

There are three transit compartments for HbA1c. The first transit compartment is shown in Eq. 8 and the remaining transit compartments can be seen in the NONMEM control stream (Supplementary data). Postprandial glucose (PPG) was not measured, however it may contribute to the production of HbA1c in addition to FPG. The potential contribution of PPG, therefore was estimated. At t > 0, the effect of PPG was scaled by a scaling parameter ($Scale_{PPG}$, Eq. 8).

$$dHbA1c(1)/_{dt} = HbA1c_{kin} \times PPG \times Scale_{PPG} \times FPG - HbA1c_{kout}$$

Eq. 8

The mean transit time (MTT) of HbA1c is estimated and $HbA1c_{kout}$ was calculated as $\frac{3}{MTT}$.

Population analyses

Population pharmacodynamic analyses were conducted using the population modelling package NONMEM® 7.2.0 (ICON Development Solutions, Hanover, MD, USA) [10] with first-order conditional estimation method with interaction (FOCE-I). Model development was managed using Perl-Speaks-NONMEM 3.5.3 [11], Pirana 2.8.1 [12] and R (Version 3.2.5) [13]. All observations were log-transformed prior to the analysis and residual variability was described with proportional error models for weight, FSI, FPG and HbA1c. The IIV for PPG, $Scale_{EFS}$, baseline WGT and residual error models were log-normally distributed, whilst all other parameters were assumed to be normally distributed. Since the structure of the model was already developed, the model building procedure included (1) exploratory data analysis and data exclusion, (2) sensitivity analyses, (3) covariate modelling and (4) model evaluation.

1. *Exploratory data analysis and data exclusion*

For Studies 2 and 3, some observations and subjects were excluded from the analyses to avoid bias. The reference range for FSI is below 25 mI U/L [14]. There was one outlying FSI observation of 343 mI U/L, indicating non-compliance with the fasting protocol. This FSI observation and the corresponding FPG were excluded from the analyses.

There were two subjects who terminated the trial on the second visit (18 days) and three subjects with only one FSI observation. These individuals were excluded from the analyses. In total, only 1% of the original dataset was excluded to avoid bias in parameter estimates. After removing these observations, the median FSI of the dataset was 14.8 mI U/L (2.7 mI U/L – 99.8 mI U/L, range).

In one arm of Study 2, subjects entered a 6-week washout phase, however, there was only one observation collected during this phase. Therefore, observations during this phase were not used for model development.

2. Sensitivity analyses

Sensitivity analyses were conducted on various system-specific parameters that were considered difficult to estimate in Studies 2 and 3. β-cell function (B, Eq. 7) involves both estimating the natural decline in β-cell function from baseline (BF, Eq. 5), which is counteracted with the positive treatment effect on β-cell function (EF_B, Eq. 6). One of the main parameters that would be difficult to estimate is r_B, the rate of β-cell function decline from baseline. The effect of fixing the population estimate of r_B to a published value of 0.209 [8] and estimating r_B was tested.

Additionally, a sensitivity analysis was also conducted on EF_B, the treatment effect on β-cell function, as it can confound the estimate of r_B. Subjects from Studies 2 and 3 did not enter a weight loss program, therefore estimates of EF_B are likely to be small or insignificant to counteract the rate of disease progression (r_B). The effect of removing EF_B to improve the estimate of $r_B$was tested.

Lastly, MTT was considered difficult to estimate due to the short trial duration of Studies 2 and 3. Therefore, the effect of fixing MTT to a previously published value of 38.9 days [8] and estimating this parameter was tested.

3. Covariate modelling

Potential covariate effects were identified by visual inspection of covariate plots against the empirical Bayes estimates (EBEs). Statistical significance was determined by stepwise inclusion into the model, and was guided by the objective function value (OFV, -2log likelihood), whereby a significance level of P <0.01 was considered statistically significant (corresponds to drop in OFV by 6.63 points with d.f.=1) [15]. The covariates investigated included age, sex, ethnicity, diabetes duration and compliance to placebo treatment (by pill count), for parameters describing the treatment effect (EF_{DE}, EF_{PL}, EF_B) and parameters describing the disease status (b_0, s_0, r_B). The duration of diabetes was not known for subjects enrolled in Study 1, and therefore was assumed to be 1 year to enable testing diabetes duration as a covariate in the model.

The potential covariate effect of diabetes duration was investigated visually using EBE plots *vs* diabetes duration for Studies 2 and 3. The disposition index was used to explore potential relationships between model-derived estimates of b_0 and s_0 with diabetes duration. The disposition index is the hyperbolic relationship between insulin sensitivity and beta-cell function (or insulin secretion), whereby a decrease in insulin sensitivity (high FPG) is compensated by an increase in β-cell function to stimulate insulin release [16].

The baseline values of body weight, FPG, FSI and HbA1c were tested as potential covariates on the parameters describing the treatment effect. The transformation of random effect parameters [17] were investigated for the random effect variables that were non-normally distributed.

Sources of inter-study variability (ISV) were investigated by inspecting plots of EBEs *vs* Study. Since Study 3 did not include a washout phase, it is possible that residual treatment effects of metformin continued in this placebo study. This was further investigated by testing

ISV as a fixed effect on baseline parameters (weight, FPG, FSI and HbA1c), on parameters describing the treatment effect (EF_{DE}, EF_{PL}, EF_{B}) and the disease status (b_0, s_0, r_B).

Model evaluation and statistical methods

Model selection was guided by a significant drop in OFV (P <0.01), goodness-of-fit plots and visual predictive checks (VPCs). Model stability was assessed by the ability of the model to achieve a successful covariance step and a low condition number (<1000, [18]). The condition number is calculated as the square root of the ratio of the largest eigenvalue to the smallest eigenvalue of the correlation matrix to evaluate collinearity of the parameters [18]. The VPC of the final model was evaluated by comparing the 10th, 50th and 90th percentiles of the observations to the corresponding 10th, 50th and 90th percentiles of the simulations (n = 1000) [19].

Significant differences between baseline measurements were evaluated using the unpaired *t* test in R. A P value of <0.001 was considered statistically significant.

RESULTS

Characteristics of the subjects

The demographics of the subjects from each study are shown in Table 2. There were significant differences in the body weight distribution for all 3 studies (Figure 1). Subjects from Study 1 had a higher baseline body weight compared to Study 2 (median difference 24.1 kg) and Study 3 (median difference 14.8 kg). The distribution of height and BMI, however, was comparable between studies. At baseline, the insulin-to-glucose ratio was lower in

Studies 2 and 3 compared to Study 1 (Table 2, Figure 1), indicating that subjects from Studies 2 and 3 had a poorer β-cell function. Furthermore, subjects enrolled in Study 3 had a longer duration of diabetes than Study 2 (median difference 3.1 years).

Population model

A total of 8587 observations from Study 1, 1526 observations from Study 2 and 1554 observations from Study 3 were used for population pharmacodynamic modelling. Like the WHIG model, a full omega block (n = 10) was used to account for all correlations between parameters (Supplementary Table S3). The covariance between the residual error of FSI and FPG was also estimated.

An ISV on weight was modelled to show a shift in the population mean for each study. From the base model, this was found to significantly improve the model (ΔOFV -88.03 points). An ISV was also added for b_0 (Study 1 vs Study 2 and 3), which was also significant (ΔOFV -88.9 points). The IIV for s_0 was non-normally distributed and was transformed using the Box-Cox transformation [17] to improve the model (ΔOFV -44.2 points, *P <0.001*):

$$\eta_{st} = \frac{\left[\left(exp^{\eta_{s_0}}\right)^{\theta_{shape}} - 1\right]}{\theta_{shape}} \quad \text{Eq. 9}$$

where η_{st} is the Box-Cox transformed random effect for s_0, η_{s_0} is the normally distributed random effect and θ_{shape} is a parameter determining the shape of the distribution. Age, diabetes duration, sex, and ethnicity were not significant covariates for these baseline parameters.

In the WHIG model, there were 2 treatment effects on weight at the placebo run-in phase and at the treatment phase. These treatment effects were kept for Study 1. The

additional placebo effect at the treatment phase for Studies 2 and 3, however, was not significant and was removed from the model. The lack of a washout phase in Study 3 did not influence the parameter estimates of treatment effects and disease status. There was an ISV added for baseline weight but this was also added for Study 2.

Compliance to placebo pills was explored as a potential covariate on the treatment effects for weight (EF_{DE}). For Study 2 and 3, the median compliance was 99.8% (61.3% – 100%, range) and 100% (87.1% - 100%), respectively. However, overall compliance to placebo treatment was not a significant covariate for the treatment effects on weight. The effect of prior treatment in Study 2 and 3 were also investigated as a covariate on the treatment effects (EF_{DE}, EF_B), but it did not result in an improvement in the model.

Sensitivity analyses

When estimated, the MTT parameter increased from 38.9 days to 53 days, corresponding to 26% lower estimate of $HbA1c_{kout}$ (0.0566 from 0.0771) and decreased OFV by -32.9 points (P <0.001). This resulted in approximately 20-30% lower estimates of the effect of post-prandial glucose (PPG) and an increase of 23% on the estimate EF_B (treatment effect on β-cell function). Therefore, estimating MTT not only indicates a slower glycosylation rate of the red blood cells, but it also shifted the contribution to the production of HbA1c from PPG to FPG (Eq. 7, by increasing the estimate of EF_B, insulin and consequently FPG). Although this resulted in a significant improvement in the OFV (-24.6 points, P <0.001), the model was ill-conditioned (eigenvalue number >5000), most likely due to the short trial duration for Studies 2 and 3. This parameter was therefore fixed to the previously published value of 38.9 days, and the shift in the relative contribution of FPG and PPG on the HbA1c was thus not considered.

The effect of estimating r_B was also tested. When estimated, the population estimate for r_B was 0.502 (ΔOFV –26.4 points), which is two-fold higher than the previous estimate of 0.209 [8]. This corresponds to a reduction in β-cell function by 12%, compared to the previous estimate of 5% per year [8]. The effect of removing the treatment effect on β-cell function (EF_B) on the estimate of r_B was tested, however the estimate of r_B remained high (0.562). Factors that may have confounded the estimate of r_B include the short trial duration and the relatively sparse number of FSI observations (4-5 per subject). Since the previous estimate of r_B was based on a long clinical trial with detailed collection of observations (n = 8587), the population estimate of r_B was fixed to 0.209 because it is a more plausible estimate of disease progression.

Model-derived estimates of s_0 and b_0 are shown in Table 4. In contrast to s_0, there were substantial differences in b_0 between studies. When grouped by diabetes duration, the disposition index revealed a decrease in the insulin-secretory response in subjects with longer diabetes duration, however there was large scatter between the groups (Figure 3).

Final model evaluation

The VPCs of the final model showed good agreement between the observations and the simulated concentrations between the studies and for each pharmacodynamic measure (Figure 2). The final parameter estimates are shown in Table 3. Except for r_B and *MTT*, all parameters were estimated with acceptable precision (residual standard error <30%) without any significant shrinkage (<30%).

DISCUSSION

The most critical factor in the emergence of T2DM is obesity, which reduces insulin sensitivity [20]. Diet and exercise is commonly recommended for newly-diagnosed subjects with T2DM and can reduce HbA1c by 1.0% [21]. Using the WHIG model, the relationship between weight change, insulin sensitivity and ultimately HbA1c can now be described mechanistically [8]. Although there are many published disease models for T2DM [22, 23], the WHIG model only requires measurements of body weight, FSI, FPG and HbA1c, all of which are collected routinely in clinical practice. This is particularly valuable for people with a longer history of T2DM who require complex treatment regimens to maintain euglycaemia.

In this study we have investigated the effect of applying the WHIG model to a wider population of people with T2DM. Although the change in body weight is proportional to the change in insulin sensitivity, an inter-study variability parameter for baseline weight was required to account for the differences in the median body weight of each study. Subjects from Study 1 had experienced the most weight loss (-3.4 [-24.3 to 5.9] kg, median [range]) from baseline, and therefore had much larger increases in insulin sensitivity (median increase in insulin sensitivity, 23.2%). In contrast, weight loss was not significant in Study 2 (-0.53 [-9.2 to 4.5] kg) and Study 3 (-1.0 [-7.6 to 9.4] kg) from baseline. Despite this, implementing the change in weight as a predictor of insulin sensitivity for Studies 2 and 3 improved the model predictions as judged by the objective function value (ΔOFV -34.4) and the agreement between the observed and simulated concentrations in FPG (Figure 2).

Subjects enrolled in Study 3 were previously treated with metformin but did not have a washout phase prior to starting the placebo trial. We have accounted for potential residual treatment effects of metformin continuing on in this study, however this did not significantly improve the model. Furthermore, the estimated treatment effects ($EF_{DE,}$ EF_B) and disease

status (b_0, s_0) were not significantly different between studies. The lack of a washout phase for Study 3, therefore was not accounted for in this model because the baseline treatment effects were comparable to the estimates from Study 2. It is possible that these subjects were no longer responding to the effects of metformin because of the study inclusion criteria (inadequately controlled on metformin for over 6 weeks).

There was very little variability in insulin sensitivity between subjects with T2DM but there were substantial differences in β-cell function (Table 4). This is in agreement with previous studies which had showed very little changes in insulin sensitivity in subjects diagnosed with T2DM, but the deterioration in β-cell function continued well after the diagnosis of T2DM [24, 25]. Subjects from Study 1 had a higher median baseline β-cell function (57%) compared to Study 2 (39.1%) and Study 3 (30.2%). Since the disease progression of β-cell function was described using a logistic decay function, subjects with a lower baseline β-cell function had lower rates of disease progression as it is not possible for subjects to have a complete loss of β-cell function. Therefore, subjects from Study 3, had the slowest rate of β-cell function loss (r_B), which may be associated with their longer history of T2DM. An inter-study variability parameter was required to account for the differences in the baseline β-cell function. Other covariates, however, were not significant in explaining the differences in β-cell function.

Diabetes duration was expected to be a significant covariate for the β-cell parameters because β-cell function typically deteriorates with diabetes duration. However, the variability in the diagnosis of T2DM may have confounded diabetes duration as a potential covariate for the disease progression parameters, i.e. while some subjects were diagnosed early, others may be diagnosed when their diabetes is already quite advanced. The mean time-lapse between onset of T2DM to the diagnosis of T2DM can vary up to 6 years [26].

In the UKPDS Study, the rate of decline of β-cell function was approximately 25% over 6 years (about 4% per year) [2, 27]. A model developed using the Belfast Study, proposed two phases (Phase A, 1.7%; Phase B, 18.2%) associated with the decline in β-cell function [24]. This is consistent with the use of the original sigmoid treatment function for EF_B (Supplementary Materials) and logistic disease progression function (BF, Eq. 5). However when r_B was estimated, the median rate of loss in baseline β-cell function was about 12%, which is much higher than the rate of β-cell function from previous studies [2, 7, 8, 27].

We have fixed the estimate of r_B to previously published values because the estimates of r_B and b_0 are influenced by FSI observations. In our dataset, FSI observations were sparse (4-5 observations per subject) compared to the other pharmacodynamic measurements and are also influenced by subjects who were not compliant with the fasting protocol. Potential outliers can be seen in Figure 3, whereby some subjects had FSI over 60 mI U/L (reference range: <30 mI U/L). These outlying FSI observations (and paired FPG concentrations) were not excluded due to the significant loss in data (>10%). Furthermore, the shrinkage was low when estimating the IIV for r_B (19%, Table 3). Studies 2 and 3 were also short trials, thus, the relationship between diabetes duration and β-cell function may become more apparent with the inclusion of people with a longer history of T2DM (>5 years).

One of the major drawbacks in describing the natural progression of T2DM is the need to investigate the untreated population due to the increased risk of diabetic complications. The Belfast Study was the only longitudinal study conducted on untreated people with T2DM [25]. Long placebo trials are uncommon, particularly in people with advanced T2DM. Therefore, future studies with longitudinal data on the treated population

may provide more insight on the relationship between disease progression and diabetes duration.

Conclusion

In this study, we have shown that the WHIG model can be applied to a wider population of people with T2DM. The change in body weight as a predictor of insulin sensitivity was a significant improvement in the model and can also be applied to people who are not obese. When the WHIG model was applied to people at varying stages of disease severity, large inter-individual variability in the β-cell function was observed but there were no statistically significant covariates to explain this variability. Since it is not possible to obtain longitudinal data of the untreated population, the application of this model to the treated population with a longer history of T2DM is necessary to further investigate the relationship between β-cell function and diabetes duration. In future, the disease-modifying properties of drugs can be investigated by comparing the treatment effects of antidiabetic drugs with the effects of placebo.

AUTHOR CONTRIBUTIONS

JKD conducted the study, analyzed the data and wrote the manuscript. WD and MD contributed to the study idea and study design. WD and WK contributed data to the study, WD and SC contributed to the analysis of the WHIG model and approved the use of the WHIG diagram for this manuscript. WD, NP, HN, and SV contributed to the interpretation of the results. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST

Top Institute Pharma (TI Pharma) received funding from partners to support the collaboration between academic and industry partners. JKD received financial support from TI Pharma for the submitted work, WD is employed by Janssen Research and Development, NP and HN are employees of Takeda Pharmaceuticals, WK is employed by Astellas Pharma Europe and SV is employed by Merck & Co. Katia Verhamme works for a group who in the past received unconditional research grants from Pfizer/Boerhringer Ingelheim, Yamanouchi, GSK and Novartis. None of which are related to the topic of this research.

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Table 1. The inclusion criteria and study design of the trials

	Study 1	Study 2		Study 3
N	181	59		64
ClinicalTrials.gov No.	NCT0023660	NCT01071850		NCT01117584
Disease status	Treatment naïve	Treatment naïve (n=28) and prior treatment (n=31)		Inadequately controlled on a daily dose of 1.5 g metformin (> 6 weeks)
BMI (kg/m^2)	27 – 50	20 - 45		
HbA1c (%)[a]	< 10.5	6.8 – 9.5		7.0 – 9.5
Diet and exercise regimen	-600kcal diet and physical activity at all visits	Reported at stable diet and exercise regimen throughout the study		
Study design				
Trial duration	66 weeks	14 weeks		
Wash-out phase	-	-	6 weeks	-
Placebo-run in	6 weeks	2 weeks		
Placebo treatment phase	60 weeks	12 weeks		
Follow-up phase	-	4 weeks		

[a] As measured at the first clinic visit.

Table 2. Baseline characteristics and estimates of subjects from each study. Data are median (IQR).

	Study 1	Study 2	Study 3
N	181	66	65
Age (y)	54 (48 – 60)	55 (48 – 60)	57 (51 - 63)
% Female	63	56	45
Height (m)	1.68 (1.62 – 1.77)	1.61 (1.56 – 1.68)	1.68 (1.60 – 1.73)
BMI (kg/m^2)	31.8 (29.1 – 35.6)	29.6 (26.6 – 33.8)	31.0 (28.9 – 34.2)
Baseline measurements			
Weight (kg)	104.2 (94.3 – 115.4)	79.3 (68.6 – 87.9)	89.0 (81.2 – 97.6)
FSI (µU/mL)	17.8 (12.3 – 27.4)	12.1 (8.2 – 18.2)	13.4 (9.1 – 21.6)
FPG (mmol/L)	7.6 (7.0 – 8.5)	7.2 (6.3 – 8.6)	8.5 (7.4 – 10.1)
HbA1c (%)	6.7 (6.3 – 7.2)	7.4 (7.1 – 7.9)	7.7 (7.2 – 8.2)
Insulin-to-glucose ratio	2.27 (1.69 – 3.01)	1.51 (1.04 – 2.18)	1.47 (1.10 – 2.44)
Diabetes duration (y)†	-	2.7 (1.3 – 4.6)	5.8 (2.9 – 8.8)

†Diabetes duration is not known for Study 1

Table 3. Final population parameter estimates from the final model. IIV, inter-individual variability (%), RSE, residual standard error.

	Parameter estimate (RSE%)	**IIV[a] (RSE%) [Shrinkage%]**
Weight		
WGT $t_{1/2}$ (days)	73.9 (5)	-
Baseline WGT (kg)	102 (1)	16.1 (4) [0]
β-cell function		
Baseline β-cell function, logistic function (b_0):		
Study 1 Study 2 and 3	-0.298 (31) 0.677 (17)	1.13 (13) [9.5]
r_B, rate of β-cell function loss per year, logistic function	0.209 (fixed)	0.408 (16) [19]
EF_{BT}, treatment effect on β-cell function (%)	0.0781 (31)	0.053 (12) [15.8]
Insulin sensitivity		
s_0, baseline insulin sensitivity, logistic function	0.963 (5)	0.485 (13) [6.4]
θ_{shape}, shape parameter for IIV distribution of s_0	-0.476 (15)	-
$Scale_{EFS}$, scaling factor for weight change on insulin sensitivity	0.0458 (9)	75.7 (10) [19.9]
HbA1c		
HbA1c k_{in}, %d L/mmol	0.0152 (3)	-
MTT, mean transit time (days)	38.9 (fixed)	-
PPG	0.057 (7)	25.6 (10) [6]
$Scale_{PPG}$	0.967 (1)	
Treatment effects		
EF_{DE}, placebo, diet and exercise effect at placebo run-in	3.0 (16)	21.3 (16) [12.3]
EF_{PL}, placebo effect at treatment phase (Study 1 only)	3.46 (16)	28.9 (18) [24.9]
EF_{LOSS}, rate of loss of placebo treatment effect (% /year)	3.76 (24)	70.4 (16) [24.1]
Residual errors		
Weight	0.0096 (1)	-
FSI	0.265 (4)	41.5 (6) [22.2]
FPG	0.0841 (4)	29 (11.3) [7.2]
HbA1c	0.0254 (3)	22 (10) [19.8]

[a]Normally distributed IIV (b_0, r_B, EF_B, s_0, EF_{DE}, EF_{PL},*DPR)* were reported as absolute values.

Table 4. Comparison of the baseline insulin sensitivity and baseline beta-cell function parameter estimates of each study. Values are median (IQR).

	Study 1	Study 2	Study 3
s_0 (%)	24.5 (19.3 – 31.9)	27.4 (20.8 – 43.1)	29.5 (20.1 – 43.1)
b_0 (%)	57.0 (40.0 – 76.5)	39.1 (25.3 – 59.5)	30.2 (19.0 – 49.2)
r_B (logistic function)	0.368 (0.149 – 0.645)	0.369 (0.043 – 0.770)	0.148 (-0.325 – 0.558)

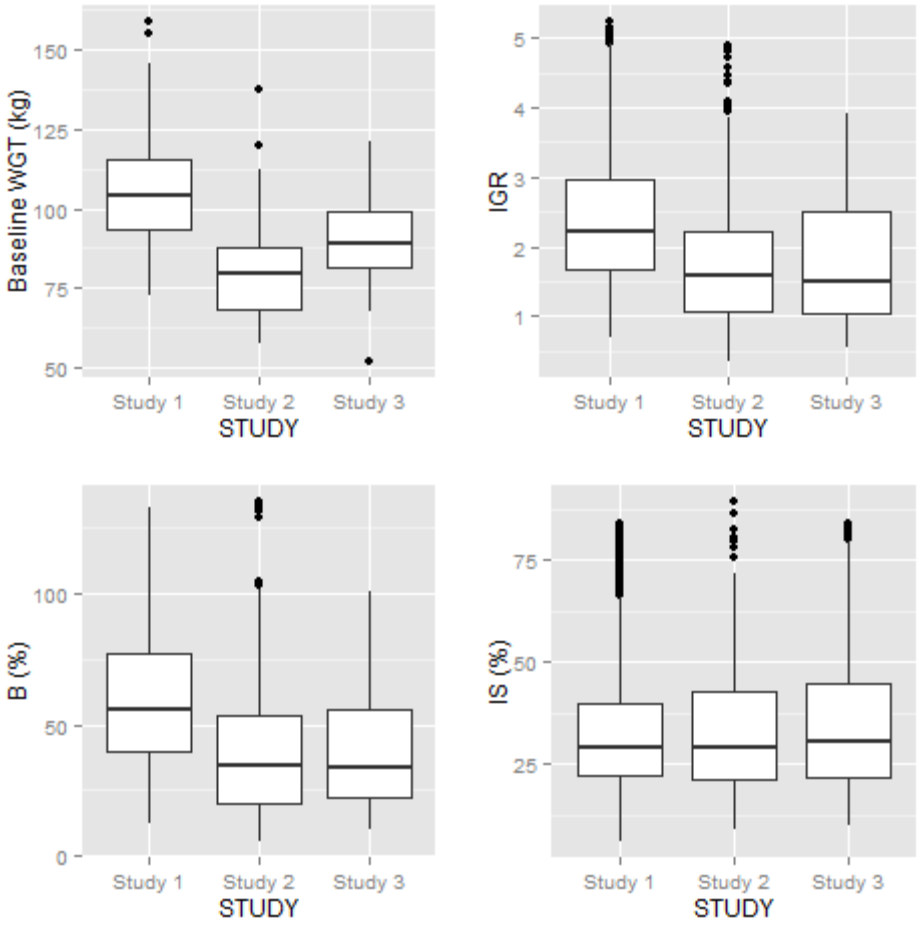

Figure 1. Inter-study variability in placebo arms (Study 1, Study 2 and Study 3). IGR, insulin/glucose ratio; B, β-cell function; IS, insulin sensitivity.

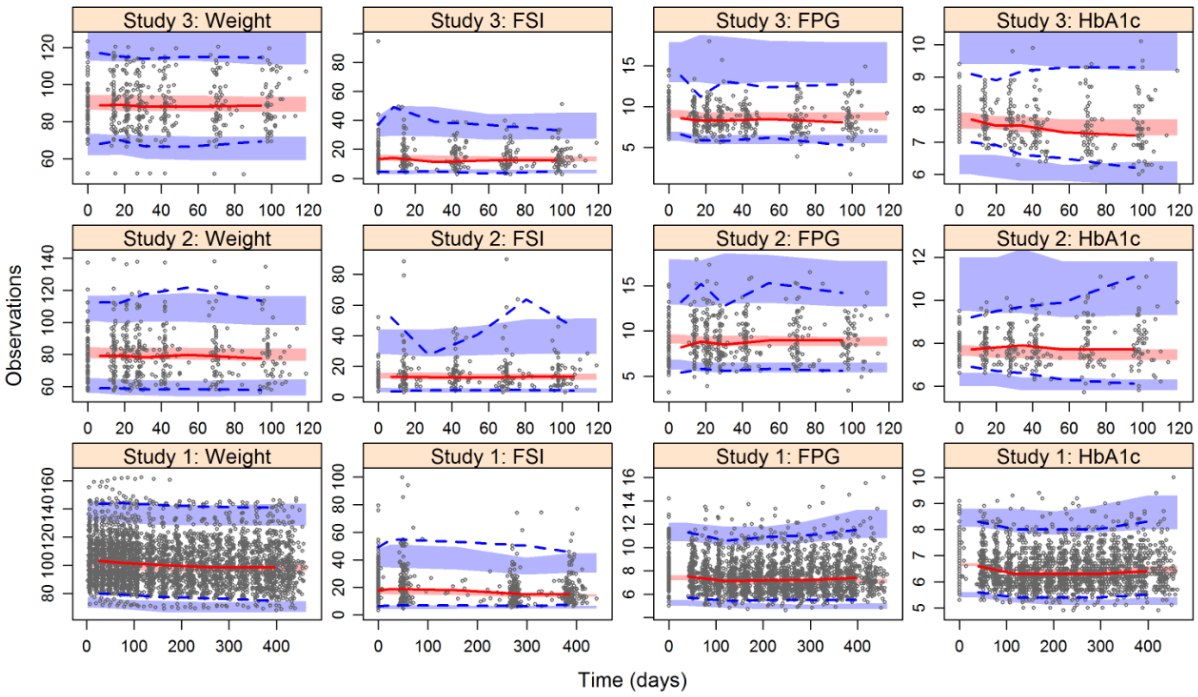

Figure 2. Visual predictive checks (VPCs) of the observations of weight, fasting serum insulin (FSI), fasting plasma glucose (FPG) and HbA1c stratified by study. The shaded areas are the 95% confidence intervals of the 10th, 50th and 90th percentiles of the simulated concentrations. The dotted lines are the 10th and 90th percentiles from the observations and the solid line is the 50th percentile of the observations. The dots are the observations.

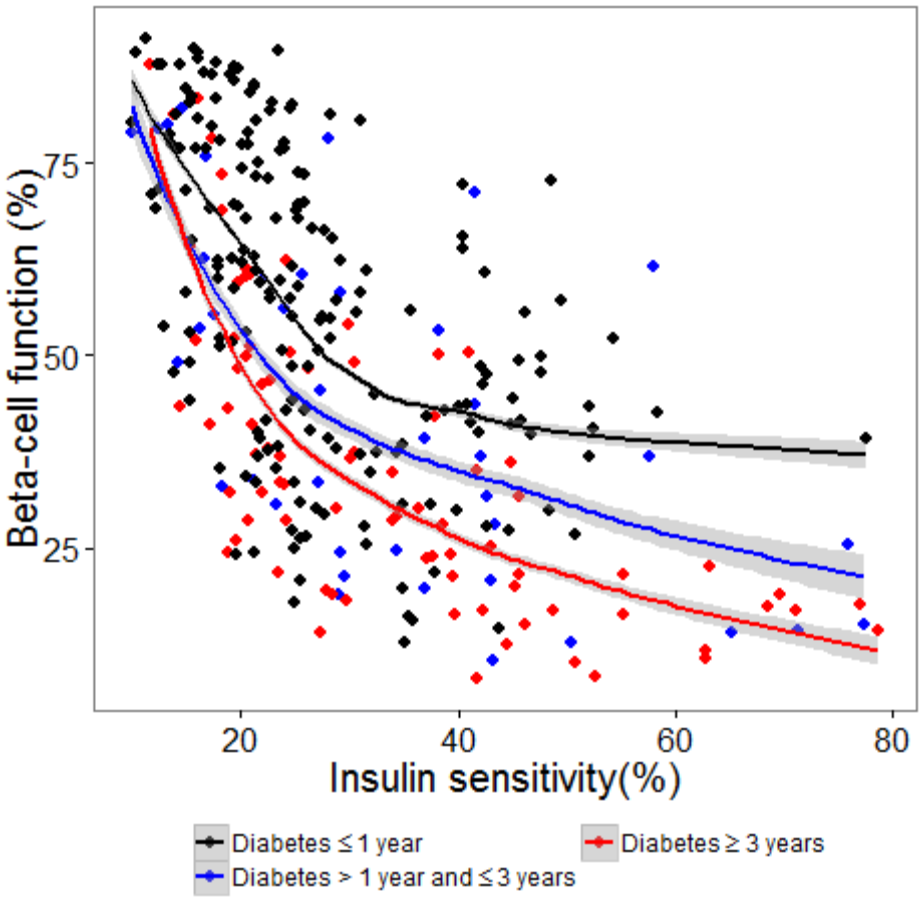

Figure 3. The disposition index of subjects grouped by their diabetes duration. A robust loess smooth curve was plotted with a 95% confidence interval around the mean.