ORIGINAL ARTICLE

Weight-HbA1c-Insulin-Glucose Model for Describing Disease Progression of Type 2 Diabetes

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A previous semi-mechanistic model described changes in fasting serum insulin (FSI), fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c) in patients with type 2 diabetic mellitus (T2DM) by modeling insulin sensitivity and β-cell function. It was later suggested that change in body weight could affect insulin sensitivity, which this study evaluated in a population model to describe the disease progression of T2DM. Nonlinear mixed effects modeling was performed on data from 181 obese patients with newly diagnosed T2DM managed with diet and exercise for 67 weeks. Baseline β-cell function and insulin sensitivity were 61% and 25% of normal, respectively. Management with diet and exercise (mean change in body weight = −4.1 kg) was associated with an increase of insulin sensitivity (30.1%) at the end of the study. Changes in insulin sensitivity were associated with a decrease of FPG (range, 7.8–7.3 mmol/L) and HbA1c (6.7–6.4%). Weight change as an effector on insulin sensitivity was successfully evaluated in a semi-mechanistic population model.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC? ☑ The existing semi-mechanistic models for modeling disease progression of type 2 diabetes have yet to account for weight change, which is a potentially important biomarker for understanding the disease. • WHAT QUESTION DID THIS STUDY ADDRESS? ☑ Weight change as an effector for insulin sensitivity has been successfully evaluated in a semi-mechanistic model which then alters the FSI-FPG homeostasis, and subsequently HbA1c. • WHAT THIS STUDY ADDS TO OUR KNOWLEDGE ☑ The study demonstrated that the added information from weight change is important in developing a disease progression model for T2DM. • HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS ☑ Having quantified the effects of weight change on insulin sensitivity, the model could be applied in various settings, such as predicting HbA1c in a long-term patient management program or in drug development.

There have been a number of models describing biomarkers of diabetes, ranging from empirical[1] to more mechanistic models.[2–4] The commonly used biomarkers for diagnosis and subsequent monitoring of disease progression are fasting plasma glucose (FPG), fasting serum insulin (FSI), and glycated hemoglobin A1c (HbA1c). These three biomarkers are the most commonly seen in long-term data as well. However, the mechanisms behind the glucose-insulin homeostasis dysfunction leading to diabetes are complex and there are many processes involved that are less studied.

The underlying processes in the disease progression of type 2 diabetes mellitus (T2DM) are the progressive loss of insulin sensitivity and β-cell function.[5] The disease onset of T2DM is initially driven by decreases in insulin sensitivity. With decreased insulin sensitivity, β-cells compensate by overproducing insulin, which leads to hyperinsulinemia, in order to keep the glucose homeostasis stable. Eventually, insulin production is diminished from relative β-cell failure because of exhaustion, and combined with decreasing insulin sensitivity then leads to hyperglycemia in T2DM.[6]

The standard of care for patients with T2DM is metformin treatment, diet, and exercise. The low-sugar diet was originally introduced as a means to reduce the glucose intake and thereby reduce plasma glucose, but it was later discovered that any diet resulting in weight loss will reduce plasma glucose concentrations independent of glucose intake.[7] It has been hypothesized that the weight loss is tightly linked to improved insulin sensitivity, such that plasma glucose concentrations decrease with maintained insulin concentrations.[8,9] de Winter et al.[10] published a mechanism-based model for T2DM that describes the disease progression and treatment effects of oral antidiabetic drugs on FSI, FPG, and HbA1c. In this model, insulin sensitivity and β-cell failure at baseline are estimated and are changing over time. The model is implemented with the homeostatic model assessment (HOMA) method such that for a given FPG and FSI the estimated insulin sensitivity and β-cell failure is predicted by HOMA-S% and HOMA-B%, respectively.[11] FSI and FPG in this model was described with a linked turnover model with an inverse relationship, whereby FSI inhibits FPG production and FPG stimulates FSI production, mimicking the physiological feedback mechanisms for insulin and glucose. FPG is then used as an input for the production of HbA1c in a single compartment.

Although this model was a conceptual improvement over previous descriptive models, insulin sensitivity was estimated empirically without underlying mechanistic support. In a later effort, it was suggested that modeling insulin

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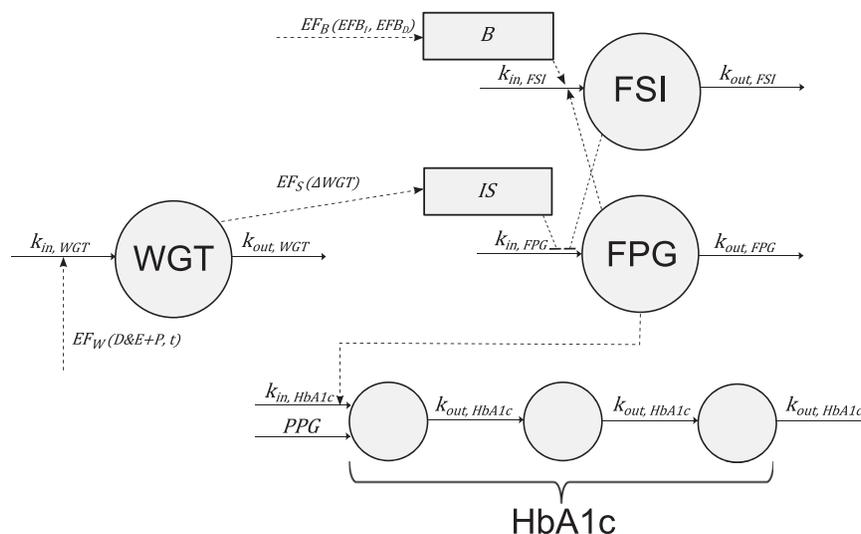
Figure 1 The weight glycated hemoglobin (HbA1c) insulin glucose (WHIG) model. EF_W is the combined treatment effect of diet and exercise (D&E), placebo (P), and an upward counter-effect dependent on time acting on the input of weight (WGT). Effect on insulin sensitivity (EF_S) is a function of change in weight (ΔWGT), which changes insulin sensitivity (IS). EF_B is the treatment effect on β-cell function, which is a composite function consisting of its increase (EFB_I) and decrease (EFB_D) over time. EF_B together with the natural progressive loss on β-cell function (B), determines the production rate of fasting serum insulin (FSI). The homeostasis of FSI and fasting plasma glucose (FPG) is described with FSI inhibiting FPG production, whereas FPG stimulates FSI production. FPG and postprandial glucose (PPG) drive the production of HbA1c, which is described using three transit compartments.

sensitivity as a mechanism-based function of change in body weight could be superior than an empirical model.[12] In this study, we evaluated this idea on a population that underwent diet and exercise, as well as including an additional postprandial glucose (PPG) factor and transit compartments to describe HbA1c formation.

METHODS
Study design
The data used in this study came from the placebo arm of a randomized, double blind, placebo-controlled, multicenter, parallel-group study (ClinicalTrails.gov identifier: NCT00236600) to determine the efficacy and safety of topiramate, an anticonvulsant drug that induces weight loss as a side effect. The placebo arm consisted of 181 (67 men, 114 women) Swedish, obese, newly diagnosed with T2DM, treatment-naive patients. The studied population was between 18 and 75 years of age with a body mass index ≥ 27 kg/m^2 and <50 kg/m^2, median baseline weight (BLWT) of 104 kg (range, 72–159 kg), median baseline FSI of 17.8 μU/mL (range, 3.3–79.5 μU/mL), median baseline FPG of 7.6 mmol/L (range, 5–14.2 mmol/L), and median baseline HbA1c of 6.7% (range, 5.3–9.1%).

The subjects underwent six weeks of placebo run-in before a randomized treatment phase (placebo arm in this case), which lasted for 60 weeks. The treatment phase was further divided into a titration phase (8 weeks) and a fixed dose maintenance phase (52 weeks). During the run-in phase, the subjects were treated with placebo and a non-pharmacologic therapy, which was continued until the end of the active treatment phase. The following data were used in the analysis: weight (kg), which was collected every two weeks during the run-in and titration phase, and every four weeks during the maintenance phase (up to 22 obser-

vations per subject), FSI collected at the start of the run-in and titration phase, and twice during the maintenance phase (up to four observations per subject), FPG collected from the start of the run-in until the end of the maintenance phase (up to 19 observations per subject), and HbA1c collected from the start of the run-in phase until the end of the maintenance phase (up to 17 observations per subject).

The ancillary nonpharmacologic therapy consisted of an individualized energy-deficient diet, a behavioral modification program, and a physical activity program explained by trained counselors was provided for all subjects from enrolment through to the final visit.

The prescribed energy-deficient diet for each subject was 600 kcal (2500 kJ) less than the individual subject's total energy expenditure, which was calculated as 1.3 times the individual's basal metabolic rate.[13] A diabetic diet with a maximum of 30% fat content was designed for each subject, and total energy expenditure was recalculated for all subjects six months (32 weeks) into the maintenance period.

Succinct model description
The weight HbA1c insulin glucose (WHIG) model (**Figure 1**) builds upon the previously published semi-mechanistic model by de Winter *et al.*[10] with an additional turnover model for body weight,[12] which has a mechanism-based relationship with insulin sensitivity. The homeostatic feedback relationship between FPG and FSI was described using linked turnover models, by which insulin sensitivity and FSI are inversely related to the production rate of FPG, because FSI has a strong inhibiting effect on hepatic glucose production, which is the primary determinant of FPG in the basal state,[14] so that increased FSI and/or insulin sensitivity results in a lower FPG. The production of FSI was governed by the FPG concentration, modulated by natural β-cell function, treatment

effect (EF_B), and their change over time. HbA1c was described using three transit compartments, with production determined by FPG with contribution from a PPG factor. Detailed descriptions of each model component are given below.

Weight change

In essence, all weight change can be described with the basic energy flux balance equation,[15] which is energy intake (I) subtracted by energy expenditure (E).

$$\frac{dWGT}{dt} = I - E \tag{1}$$

The daily rate of energy expenditure is proportional to body weight,[16] thus, subjects' diets were personalized based on their body weights. In the current study design, weight change from energy flux imbalance was achieved from a combination of diet (restricted energy intake) and exercise (increased energy expenditure), together known as diet and exercise (D&E). Although D&E should ideally be separated into two effects acting on the input (diet) and output (exercise) of weight, as described above, multiple D&E effects would be unidentifiable and therefore they have been combined as a single effect ($EF_{D\&E}$).

$$EF_{D\&E+P_i} = EF_{D\&E_i} + EF_{P_i} \tag{2}$$

$EF_{D\&E+P}$ is the sum of the parameters describing diet and exercise and placebo (EF_P) for each individual (*i*). These parameters, normally distributed with mean of $\Theta_{D\&E}$ and Θ_P and standard deviation (SD) of $\omega_{D\&E}$ and ω_P are modeled as step functions with the effect setting in at week zero and week six, respectively. $EF_{D\&E+P}$ is therefore the total negative contribution to the overall effect on weight (EF_W).

Over time, there is also a constant positive contribution on weight, attributed to the lack of motivation to continue diet and exercise and/or placebo effect wearing off, EF_{UP}. EF_{UP} is assumed to be a normally distributed parameter with mean Θ_{UP} and SD ω_{UP}; thus EF_{UP}, even though having a positive median, can take both positive and negative values on an individual level, indicating a weight loss or gain, respectively.

The net effect on weight input (EF_W) is therefore the product of EF_{UP} and $EF_{D\&E+P}$, both normalized to one at time zero. Assuming a steady-state, weight input is equal to weight output, so EF_W below one will result in weight loss.

$$EF_W = \frac{100 + EF_{UP,i} \cdot t/365}{100} \cdot \frac{100 - EF_{D\&E+P,i}}{100} \tag{3}$$

$$\frac{dWGT}{dt} = EF_W \cdot Kin_{WGT} - Kout_{WT} \cdot WGT \tag{4}$$

Insulin sensitivity

Changes in insulin sensitivity were modeled as inversely proportional to an individual's absolute change in weight (ΔWGT; Eq. 5). Effect on insulin sensitivity (EF_S) is then expressed as a fraction that is scaled linearly ($Scale_{EFS}$) to ΔWGT (Eq. 6). Individual baseline weight ($BLWT_i$) and $Scale_{EFs,i}$ were estimated with a log-normal distribution with a mean of Θ_{BLWT} and $\Theta_{ScaleEFs,i}$ and a SD of ω_{BLWT} and $\omega_{ScaleEFs,i}$. The more an individual loses weight, the higher the insulin sensitivity and, conversely, the more an individual gains in weight, the lower the insulin sensitivity.

$$\Delta WGT = BLWT_i - WGT \tag{5}$$

$$EF_S = 1 + Scale_{EFs,i} \cdot \Delta WGT \tag{6}$$

β-cell function and disease progression

The rate of natural disease progression of β-cell function deterioration (RB) was modeled as a logistic decline from baseline β-cell function (B_0) per year, and is normally distributed with a mean of Θ_{B0} and Θ_{RB} and a SD of ω_{B0} and ω_{RB}, respectively.

$$B = \frac{1}{1 + e^{B_{0,i} + RB_i \cdot t/365}} \tag{7}$$

An empirical treatment effect (EF_B) is multiplied with the natural β-cell function to mimic the natural response of the β-cells to stimulate insulin release in order to compensate for reduced insulin sensitivity in early stages of T2DM. EF_B is a composite function comprising of a logistic increase (EFB_I) using the start of treatment date (t_{TRT}) as the half increase time with a steepness parameter (SEFBI), and a logistic decline (EFB_D) that eliminates the effect with both the time at half decline (EFB_{50}) and steepness (SEFBD) estimated. EF_B increases from one and then back to one over the course of the study duration.

$$EFB_I = \left(\frac{EF_{B,max,i}}{1 + \left(\frac{t}{t_{TRT,i}}\right)^{SEFBI}} \right) \tag{8}$$

$$EFB_D = \left(\frac{EFB_{I,i}}{1 + \left(\frac{t}{EFB_{50,i}}\right)^{SEFBD}} \right) \tag{9}$$

$$EF_B = 1 + EFB_D \tag{10}$$

The maximal relative increase of β-cell function ($EF_{B,max,i}$) and the time of half decline ($EFB_{50,i}$) are log-normally distributed with a mean of Θ_{EFBmax} and Θ_{EFB50} and a SD of ω_{EFBmax} and ω_{EFB50}, respectively.

FSI-FPG homeostatic feedback model

The homeostasis between FSI and FPG is biologically complex and involves many processes, and could become even more complicated with an active treatment. In the WHIG model, the relationship between FSI and FPG are described with the following differential equations[10]:

$$\frac{dFSI}{dt} = EF_B \cdot B \cdot (FPG\text{-}3.5) \cdot Kin_{FSI} - FSI \cdot Kout_{FSI} \tag{11}$$

$$\frac{dFPG}{dt} = \frac{Kin_{FPG}}{EF_S \cdot IS_0 \cdot FSI} - FPG \cdot Kout_{FPG} \tag{12}$$

The production rate of FSI is stimulated by FPG, but also negatively affected by natural disease progression leading to

the loss of β-cell function. FSI production could be further modified by a treatment effect (EF_B; Eq. 10). For consistency with the HOMA equations, a lower physiological limit of 3.5 mmol/L for FPG-stimulated insulin secretion was used.[17,18] Therefore, IS_0 is the estimated baseline insulin sensitivity with a normal distribution with a mean of Θ_{IS0} and a SD of ω_{IS0}, which is then expressed as an inverse logit.

To speed up the modeling of these computationally intensive processes, short-term dynamics for both FSI and FPG are assumed to be at steady-state (SS; i.e., dA/dt = 0), and FSI production can be linearized with the quadratic equation (see **Supplementary Appendix S1** online). $Kin_{FSI}/Kout_{FSI}$ is a constant 7.8, corresponding to a healthy FSI_{SS} of 7.8 uU/mL, which according to the updated HOMA2 is defined as the concentration of insulin that will have $\sim$100% insulin sensitivity.[18] $Kin_{FPG}/Kout_{FPG}$ is a constant with value 35.1, calculated as a product from healthy FPG_{SS} of 4.5 mmol/L given a FSI_{SS} of 7.8 uU/mL.

HbA1c model

The total amount of HbA1c is given by the sum of three transit compartments (Eq. 13). The rate of Hb glycation is driven by FPG, in addition to a residual rate that is independent of FPG, which is best explained as the contribution from PPG as well as an assay error.[19,20] The PPG effect is log-normally distributed with a mean of Θ_{PPG} and a SD of ω_{PPG}. At times greater than zero, PPG contribution is reduced by an estimated scaling parameter ($Scale_{PPG}$) that represents a PPG-lowering effect from diet and exercise (Eq. 14). The population Kin_{HbA1c} is estimated, and $Kout_{HbA1c}$ is expressed as the number of transit compartments (3) divided by the population mean transit time (MTT; Eq. 17).

$$HbA1c_{Total} = HbA1c_{cmt\ 1} + HbA1c_{cmt\ 2} + HbA1c_{cmt\ 3} \qquad (13)$$

Where

$$\frac{dHbA1c_{cmt\ 1}}{dt} = PPG_i \cdot Scale_{PPG} + Kin_{HbA1c} \cdot FPG - Kout_{HbA1c} \cdot HbA1c_{cmt\ 1}$$

$$\qquad (14)$$

$$\frac{dHbA1c_{cmt\ 2}}{dt} = Kout_{HbA1c} \cdot HbA1c_{cmt\ 1} - Kout_{HbA1c} \cdot HbA1c_{cmt\ 2}$$

$$\qquad (15)$$

$$\frac{dHbA1c_{cmt\ 3}}{dt} = Kout_{HbA1c} \cdot HbA1c_{cmt\ 2} - Kout_{HbA1c} \cdot HbA1c_{cmt\ 3}$$

$$\qquad (16)$$

$$Kout_{HbA1c} = \frac{3}{\theta_{MTT}} \qquad (17)$$

Data analysis and model evaluation

Nonlinear mixed effects modeling using NONMEM 7.2 with first order conditional estimation method with interaction (FOCE+I) was used for data analysis.[21] Model selection was based on mechanistic plausibility of its parameter val-
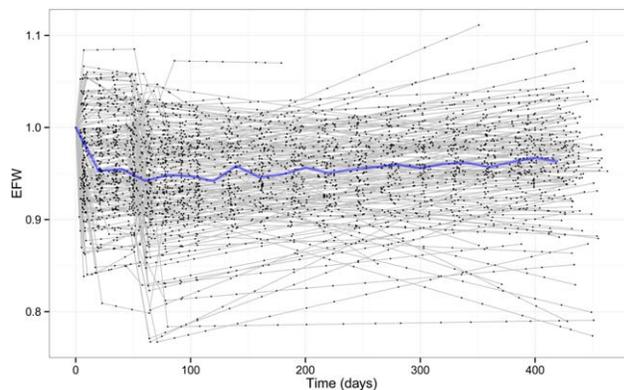

Figure 2 The estimated overall treatment effect on weight (EF_W). Black dots are post hoc estimations from the WHIG model corresponding to an observation at that time point, joined by a gray line representing each individual. The blue line represents the median value per 20-day bins. Diet and exercise effect ($EF_{D\&E}$) was modeled as an immediate step effect starting from time = 0, and the placebo effect (EF_P) comes in later at the commencement of the active treatment phase around weeks six to seven. There is also a counter-effect (EF_{UP}) that determines the slope over time.

ues, and drop in the objective function value. Objective function value is a goodness-of-fit measurement proportional to minus twice the log likelihood. When comparing nested models, a significant improvement in goodness-of-fit can be concluded if the decrease in objective function value is larger than predicted by the χ^2 distribution with degrees of freedom given by the number of parameters differing between the models.

Graphical assessment was performed using visual predictive checks (VPC). VPCs can be used to assess model fit by overlaying simulated datasets created from the model onto actual observations. In this way, discrepancies between the model and the data can be easily identified. Similar profiles between the simulated datasets and the observations indicate an adequate model. For the VPCs used in this study, the median and 95% prediction intervals based on 1,000 simulated datasets from the model were compared to the corresponding median, 2.5th, and 97.5th percentiles of the observed data. Model precision was assessed with relative standard errors obtained from a nonparametric bootstrap resampling of the final model ($n = 500$).

RESULTS

Weight change

The estimated BLWT of the study population was 104 kg. At the end of the study, the subjects on average had a 4% decrease in body weight. Predicted weight was affected by EF_W, which had an overall weight loss effect (**Figure 2**). The model fit was assessed with VPCs, which shows both the absolute values and the relative change from baseline of weight over time (**Figures 3a and 4a**). Estimated parameter values for the diet and exercise effect, placebo effect, and the weight gain counter-effect are shown in **Table 1**.
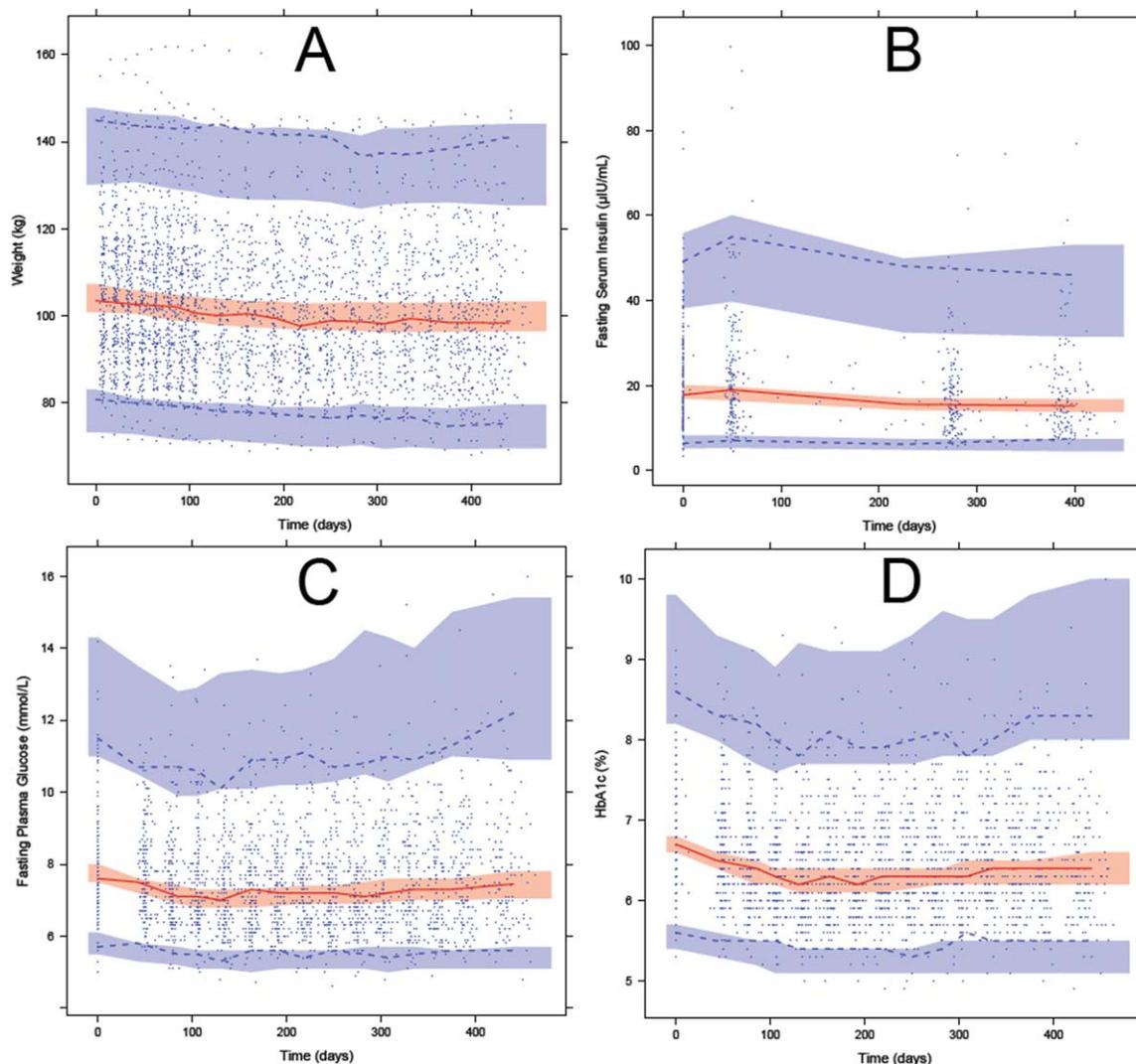
Figure 3 Visual predictive check of the biomarkers measured in the study population using the WHIG model. Blue circles indicate observations; red solid line indicate the median observations; dashed lines indicate the 97.5th and 2.5th percentiles of the observations; shaded areas indicate the 95% confidence intervals for the median (red), 97.5th and 2.5th percentiles (blue) from 1,000 simulated datasets. (**a**) Weight (kg) over time. (**b**) FSI (μIU/mL) over time. (**c**) FPG (mmol/L) over time. (**d**) HbA1c (%) over time.

Insulin sensitivity

The estimated baseline insulin sensitivity (IS_0) was 25% of normal. At the end of the study, the population insulin sensitivity increased from 25% to 30.1% of normal as a result of weight change (mean ΔWGT = 4.1 kg; **Figure 5**).

β-cell function and disease progression

The estimated baseline β-cell function (B_0) in the study population was 61% of normal and the natural disease progression rate was estimated to be 5% reduction of starting β-cell function per year. The shape of the empirical treatment effect EF_B is seen in **Figure 6a**.

The overall trend in β-cell function, which is the natural disease progression of β-cell function modified by treatment effect EF_B, shows a small initial increase at the start of the study and returning to the baseline around day 300. The

flexibility of the function allows for highly variable individual profiles of the β-cell function, shown in **Figure 6b**.

FSI change

The estimated baseline FSI was 19.2 μIU/mL and at the end of the study the mean decrease of FSI was 3.3 μIU/mL. Observations of FSI were sparse and highly variable with some FSI measurements being physiologically implausible (**Figures 3b and 4b**). If subjects did not adhere strictly to fasting before their measurements, high FSI was expected in combination with high FPG, and thus the correlation between FPG and FSI was investigated for those points with FSI >40 μIU/mL. Because the correlation was weak (R^2 = 0.0051), the high FSI observations were included in the analysis.
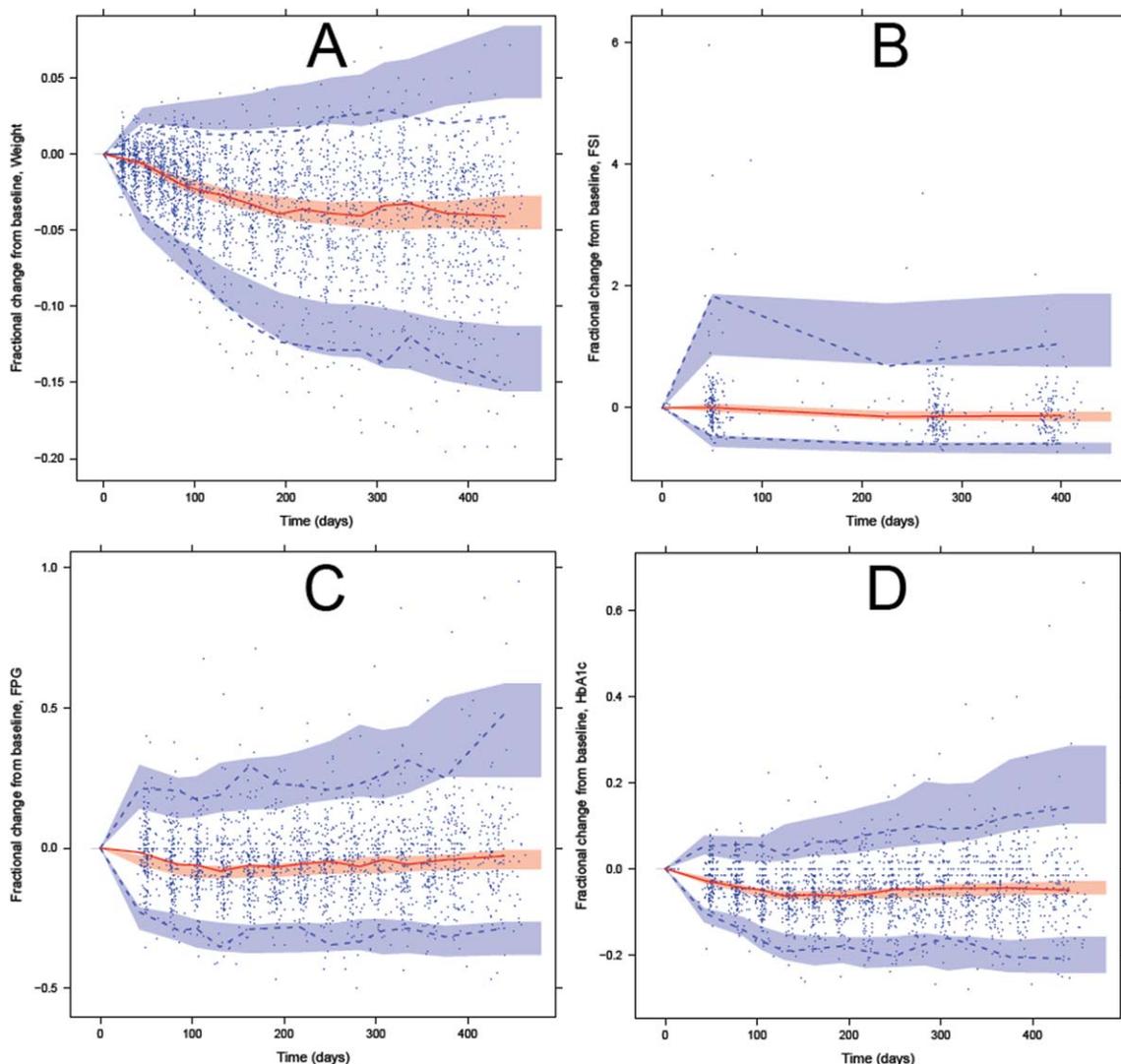
Figure 4 Visual predictive checks of change from baseline of the biomarkers measured in the study population using the WHIG model. Blue circles indicate observations; red solid line indicate the median observations; dashed lines indicate the 97.5th and 2.5th percentiles of the observations; shaded areas indicate the 95% confidence intervals for the median (red), 97.5th and 2.5th percentiles (blue) from 1,000 simulated datasets. (**a**) Fractional change of weight over time. (**b**) Fractional change of FSI over time. (**c**) Fractional change of FPG over time. (**d**) Fractional change of HbA1c over time.

FPG change

The estimated baseline FPG was 7.8 mmol/L. At the end of the study, the mean decrease of FPG was 0.4 mmol/L. This apparently small difference is related to the opposing actions of weight loss (which led to increased insulin sensitivity) and β-cell function decline (which led to decreased insulin production). The maximal decrease in FPG coincides with maximal insulin sensitivity around day 120, after which it returns back to near baseline levels at the end of the study (**Figures 3c and 4c**).

HbA1c change

The estimated baseline HbA1c was 6.7%. At the end of the study, the estimated mean decrease of HbA1c was 0.3%. If FPG is assumed as being the only factor driving HbA1c change, the change of FPG was expected to be quicker than and precede the change in HbA1c. However, this is not what was observed in the data (**Figures 3d and 4d**). To account for the similar rate of change in HbA1c and FPG and the less than expected delay in HbA1c change, an additional effect was added to the input of HbA1c glycation, which was modeled as the PPG contribution factor, and was estimated to be 0.0709% per day. At times after zero, PPG is further reduced by about 4% because of the reduced PPG contribution as a result of diet and exercise efforts. MTT across the HbA1c compartments was estimated to be 38.9 days.

The collected measurements of HbA1c values were rounded to 0.1%, which can be seen in **Figures 3d and 4d** as semidiscrete HbA1c values. To ensure the predictions in simulated datasets were similar to observed, predictions were also rounded to the closest 0.1%.

Table 1 Final parameter estimates with relative standard errors (RSE; %) and their respective interindividual variability (CV, %) of the WHIG model

Parameter	Description	Typical value (RSE)	CV[a,b] (RSE)[c]
Weight			
$t_{1/2}$, WGT, d	Half-life of weight compartment	96.9 (27.1)	–
BLWT, kg	Baseline weight	104 (1.1)	14.6 (5.2)
Insulin sensitivity			
IS_0	Baseline insulin sensitivity, logistic function	1.1 (4.3)	0.305 (6.4)
Scale EF_S	Scaling factor of change in weight on insulin sensitivity	0.0514 (11.9)	67 (11.7)
β-cell function			
B_0	Baseline β-cell function, logistic function	−0.446 (25.1)	1.4 (7.6)
EFB, max	Maximal relative increase of β-cell function	0.171 (12.4)	49.9 (20.9)
$SEFB_I$	Shape parameter for logistic increase of β-cell function	−3.69 (25.9)	–
$SEFB_D$	Shape parameter for logistic decrease of β-cell function	8.05 (28.0)	–
EFB50, d	Time at half of EFB logistic decline	190 (6.0)	34.9 (11.4)
RB, y	Rate of baseline β-cell function decrease per year, logits	0.209 (34.9)	0.21 (18.3)
HbA1c			
MTT, d	Mean transit time of HbA1c	38.9 (8.7)	–
Kin, HbA1c, %/d L/mmol	Rate constant, HbA1c compartments production	0.0129 (10.2)	–
PPG, %/d	Residual HbA1c production rate independent of FPG	0.0709 (9.9)	15.4 (9.0)
Scale PPG	Scaling factor on PPG when time >0	0.963 (0.9)	–
Treatment effects			
EF_{DE}, %	Effect of diet and exercise at run-in phase on weight input	4.08 (29.1)	35.6 (28.9)
EF_R %	Effect of placebo at active treatment phase on weight input	2.28 (28.9)	40.2 (35.3)
EF_{UP} %/y	Counter-effect on weight input per year	2.99 (52.3)	74.4 (34.7)
Residual errors			
Weight	Proportional residual error for weight	0.00919 (4.2)	–
FSI	Proportional residual error for FSI	0.262 (5.4)	31.5 (16.3)
FPG	Proportional residual error for FPG	0.0688 (2.8)	25.6 (9.2)
HbA1c	Proportional residual error for HbA1c	0.0241 (2.3)	16.1 (23.7)

[a]Correlations between interindividual variabilities are found in **Supplementary Appendix S2** online.
[b]CVs for IS_0, B_0, RB, EF_{DE}, EF_R and EF_{UP} are reported as absolute values.
[c]RSEs were obtained from a nonparametric bootstrap resampling ($n = 500$) of the final model.
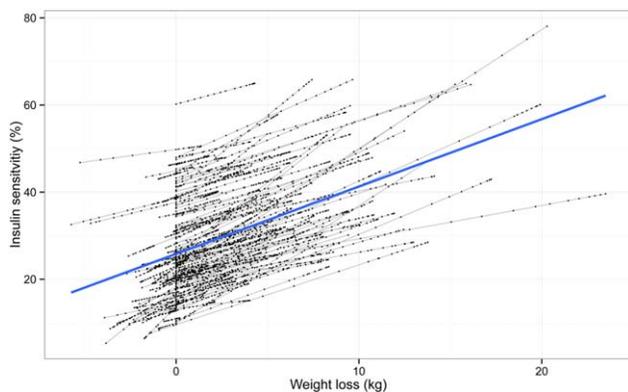

Figure 5 The relationship between weight loss and insulin sensitivity. Black dots are post hoc estimations from the WHIG model corresponding to an observation at that time point, joined by a gray line representing each individual. The blue line represents a linear regression of all points. In the WHIG model, weight loss and insulin sensitivity are linearly proportional. For each kilogram lost, an individual is expected to regain about 1.5% insulin sensitivity.

DISCUSSION

In the present study, we have evaluated the concept of using weight change as a driver for insulin sensitivity in a semi-mechanistic model, subsequently using changes in insulin sensitivity to describe FSI, FPG, and HbA1c in a diabetic population. In the WHIG model, the mechanism-based relationship between body weight change and insulin sensitivity was implemented as a linear function scaled to absolute weight change, which could be problematic if a patient had instead gained more than 10 kg in weight, as this would result in a negative insulin sensitivity. Although this was not an issue in our current study, a nonlinear function, such as an Emax function, would ensure a non-negative insulin sensitivity when extrapolating beyond the data we used for modeling. Several different implementations were also investigated, such as other nonlinear relationships between ΔWT and insulin sensitivity, as well as using absolute vs. proportional weight change, or using weight change to affect β-cell function. However, because of model stability and runtime concerns, using a linear function were found to be most appropriate.
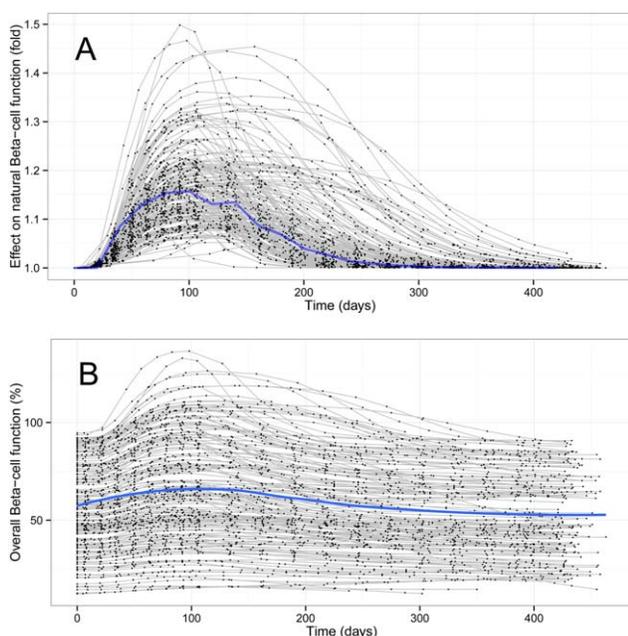
Figure 6 The predicted β-cell function of the study population using the WHIG model. Black dots are *post hoc* estimations from the WHIG model corresponding to an observation at that time point, joined by a gray line representing each individual. The blue line represents the typical individual profile from the parameter estimates. (**a**) The empirical treatment effect EF_B mimics the surge in β-cell function typically seen in new patients with T2DM. (**b**) The net effect of β-cell function over time, which is the product of the treatment effect EF_B and natural β-cell function.

Our study population had an overall small weight change (-4%), and because weight change affects insulin sensitivity and subsequently FPG, FSI, and HbA1c in the model, it is expected that our model will not produce large changes in the biomarkers relative to their baseline (**Figures 3 and 4**). This was a study design issue that could be rectified in a future study—for example, a more strict diet regimen for the subjects or conducting a longer duration study could both potentially produce larger weight changes to test the validity of the model. It was seen in our model that at the end of study duration, FPG and HbA1c were trending upward back to near baseline levels, and so it would be motivating to have data coming from a study with longer duration, for example, longer than five years, to compare how FPG and HbA1c progresses with time to the WHIG model. Another study design issue was that the diet and exercise effect could not be separately identified into a diet effect and an exercise effect. Exercise and diet could potentially have a different rate as well as site of action on affecting weight, but, in practice, it would be difficult to isolate the processes. Therefore, for the purposes of this study, combining both effects together as an input for weight was acceptable.

There were also other adaptations for the WHIG model compared to the de Winter model apart from weight. In the original model, HbA1c was estimated as a single compartment. Recent advances in red blood cell (RBC) and HbA1c modeling has suggested that using between 4 and 12 transit compartments[19,20,22] was more suitable to model the lifespan

of HbA1c. To reflect this finding, the WHIG model incorporated transit compartments for HbA1c. The number of optimal transit compartments for HbA1c was investigated but it was found that having more than three transit compartments were not significantly better objective function value-wise but had a drastically increased runtime. Therefore, as a compromise between model runtimes and stability, the decision was made to include three transit compartments for the final model.

Other structural models for HbA1c were also investigated in the model building process, which included a transitional glycosylation RBC model,[22] a mean plasma glucose RBC model,[20] and an mean plasma glucose-HbA1c model,[23] in addition to other unpublished models, such as fractional and flexible glycation rates, but none of these candidate models offered an improvement in model fit (results not shown). It is also worthwhile to note that the estimated MTT in the current model is about 40 days, whereas the lifespan of RBCs is conventionally accepted at 90–120 days. This is because the MTT in the WHIG model reflects the lifespan of glycated RBCs, rather than the natural lifespan of RBCs, therefore, our estimate reflects the postglycation lifespan of RBCs, so a better comparison would be to the mean age of circulating RBCs, which has been found to be 39–56 days in a diabetic population.[24] In addition, there was an apparent lack of delay between the times when HbA1c starts to decrease compared to FPG. Even though our model tried to account for this discrepancy with a PPG effect, there could be other confounders that were not identified, such as the patients not being at steady state of glycation at the start of the study. This is reasonable because the patients are newly diagnosed, which would lead to an HbA1c change from changes in FPG preceding the start of the study, such as drastic lifestyle changes immediately postdiagnosis. Another possible factor is the effect of exercise, which is known to contribute to hemolysis by mechanical stress,[25] which would also reduce the average lifespan, making HbA1c respond quicker to changes in glucose and reduce HbA1c overall. This possibility of hemodestruction was also explored in our analysis as an additional first-order elimination on HbA1c, but was not included in our final model due to lack of improvement.

Apart from the structural parameters, there were also changes to the stochastic or random effect parameters. In the original model, there were three covariances. In the WHIG model, the size of the variance-covariance matrix had been increased to 10 (see **Supplementary Appendix S2** online). In addition, the correlation between the residual error of FSI and FPG were also estimated. Implementing a large variance-covariance matrix had a noticeable effect of reducing the variability of the upper and lower prediction intervals (blue areas in **Figures 3 and 4**).

The model was built using data from an obese population that was newly diagnosed with T2DM, which is only a part of the entire T2DM population. Applying the model on different demographics, such as non-obese patients or patients with a long history of T2DM is the next logical step. Comparing the differences in the structural parameters between various demographics would be beneficial to both validate the model as well as providing insight to how the disease progression of T2DM differs between subpopulations.

Previously published population models on T2DM have so far not investigated the importance of using weight change as an effector for FSI-FPG homeostasis. Given that obesity is a primary risk factor and generally regarded as the main driver for T2DM, which is a lifelong disease, patients often undergo weight change over the course of their lives from lifestyle adjustments. The main advantage of the WHIG model is that it is able to use a previously neglected biomarker to predict how it will affect HbA1c with a physiological basis, which is by changing insulin sensitivity.

In conclusion, the addition of weight change as an effector was evaluated and successfully implemented to the semi-mechanistic disease progression model for T2DM. To the authors' knowledge, this was the first thorough study in which weight change was implemented in a semi-mechanistic model to quantify its effects on insulin sensitivity to predict the changes of fasting plasma glucose, fasting serum insulin, and HbA1c in humans with T2DM. As T2DM is intricately linked with obesity, further application of this updated model could prove useful in understanding the disease.

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