Expansion of the Homeostasis Model Assessment of β-Cell Function and Insulin Resistance to Enable Clinical Trial Outcome Modeling Through the Interactive Adjustment of Physiology and Treatment Effects—iHOMA2

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OBJECTIVE—To describe and make available an interactive, 24-variable homeostasis model assessment (iHOMA2) that extends the HOMA2 model, enabling the modeling of physiology and treatment effects, to present equations of the HOMA2 and iHOMA2 models, and to exemplify iHOMA2 in two widely differing scenarios: changes in insulin sensitivity with thiazolidinediones and changes in renal threshold with sodium glucose transporter (SGLT2) inhibition.

RESEARCH DESIGN AND METHODS—iHOMA2 enables a user of the available software to examine and modify the mathematical functions describing the organs and tissues involved in the glucose and hormonal compartments. We exemplify this with SGLT2 inhibition modeling (by changing the renal threshold parameters) using published data of renal effect, showing that the modeled effect is concordant with the effects on fasting glucose from independent data.

RESULTS—iHOMA2 modeling of thiazolidinediones effect suggested that changes in insulin sensitivity in the fasting state are predominantly hepatic. SGLT2 inhibition modeled by iHOMA2 resulted in a decrease in mean glucose of 1.1 mmol/L. Observed data showed a decrease in glucose of 0.9 mmol/L. There was no significant difference between the model and the independent data. Manipulation of iHOMA2s renal excretion threshold variable suggested that a decrease of 17% was required to obtain a 0.9 mmol/L decrease in mean glucose.

CONCLUSIONS—iHOMA2 is an extended mathematical model for the assessment of insulin resistance and β-cell function. The model can be used to evaluate therapeutic agents and predict effects on fasting glucose and insulin and on β-cell function and insulin sensitivity.

Type 2 diabetes is caused by a combination of progressive β-cell dysfunction, relative insulin deficiency, and variable degrees of insulin resistance that lead to dysregulation of glucose homeostasis. Understanding the biochemistry, phenotypic details, and genetic mechanisms contributing to this can yield important information on pathophysiology. The progressive nature of the disease, as well as measuring the rate of deterioration, has presented an ongoing challenge to clinicians and scientists alike. Tools to track β-cell functional changes and insulin resistance fall into three broad categories: measures of glycemic status (e.g., fasting glucose, HbA1c), physiological investigations (e.g., clamp techniques [1,2], glucose tolerance tests), and mathematical modeling (e.g., minimal model [3], Mari model [4,5], homeostasis model assessment [HOMA] [6–9]).

No single approach proved sufficient, either, for a comprehensive quantitative description of β-cell dysfunction or insulin resistance. Measures of these parameters vary depending on whether measurements are from basal or stimulated or fasting or postprandial subjects and whether pharmaceutical agents are being taken. Physiological techniques, ranging from simple glucose tolerance tests to euglycemic clamps and stable isotope studies, require expertise and are time and resource intensive, limiting their use to relatively small numbers of subjects (10). Mathematical modeling techniques also vary in their physiological assumptions. Computer-based solutions from clinical interventions (e.g., oral glucose tolerance tests with “minimal model” readout) have limitations because of the high number of samples required from each subject. Simpler modeling methods (e.g., HOMA2) use paired fasting plasma insulin and glucose concentrations to derive data on β-cell function and insulin sensitivity. HOMA2 yields a single readout of β-cell function and insulin resistance for each subject and has the advantage that, since it only requires paired basal insulin and glucose measurements, it can be used in large epidemiological and pharmaceutical studies.

One disadvantage with HOMA2 is that it is not an appropriate model to use when evaluating treatments that have similar functional effects on blood glucose but different modes of action. For example, in HOMA2 β-cell function is characterized internal to the model as a sigmoidal dose response curve relating insulin secretion to the prevailing glucose concentration. The shape of this
 sigmoidal curve is modeled using two principal variables, one of which describes the rate of insulin secretion ($K_m$) and one that describes the maximal insulin secretion ($V_{max}$). In HOMA2, changes in $b$-cell function, altering insulin secretion, are entirely attributed to changes in $V_{max}$ and $K_m$ in the basal state (11). This modeling of $b$-cell function has been a good approximation, but a comprehensive description of the $b$-cell dynamics requires more variables (11). The $b$-cell functional changes caused by sulfonylureas (12) have different dose response changes and characteristics from those induced by incretin hormones (13). Similarly, total body insulin sensitivity, defined as net glucose clearance for any given insulin concentration, cannot be comprehensively described using one fixed function as it is in HOMA2. Hepatic insulin sensitivity may differ from peripheral sensitivity, and change in glucose clearance can be completely unrelated to either hepatic or peripheral sensitivity as in the case of sodium glucose transporter 2 (SGLT2) inhibition (14). The invariant nature of HOMA2 does not allow a sufficient description for other organs and tissues involved in glucose homeostasis, and this can be important where there is knowledge of changed function, e.g., in the liver, which could be used to improve model outputs.

We have developed an interactive, 24-variable model (termed iHOMA2) that addresses problems associated with the fixed assumptions within HOMA2. Here, we describe the model in cartoon, graphical, and mathematical detail; discuss how it can be used and manipulated; present an explicit example of its use to model changes in renal threshold induced by blockade of glucose reabsorption by SGLT2 inhibition; and show how this affects the modeled fasting glucose. The model is available on open access.

**RESEARCH DESIGN AND METHODS**

**Model development**

The iHOMA2 model is shown in Fig. 1 as graphical (A), box diagrammatic (B), and mathematical (C), respectively. iHOMA2 is an integrated computer-based mathematical model of glucose and hormonal interaction under homeostatic conditions. The model, now available online at http://www.ihoma.co.uk, runs in real time with 24 operator-controlled variables (Table 1) and graphical output displays. The baseline characteristics were built from those used in the original HOMA2 model, with all of the dose-response variables now explicit. iHOMA2 runs interactively and exactly for each calculation. iHOMA2 in its default start-up setting gives identical readings to HOMA2 and can be used as a direct substitute for HOMA2 in this mode. The operator can modify each of the variables using an interactive sliding control display. The operator can control every aspect of the dose-response curve. For example, the $b$-cell characteristics are described by $P_1$–$P_5$, each of these being independently adjustable. This allows “what if” scenarios to be explored: “What would be the effect on glucose if $V_{max}$ of $b$-cell function were 50%?” “How might that be modified if the dose response curve were shifted to the left?” “What if autonomous insulin secretion continued at low blood glucose?” Similarly, the functions relating to the other organs and tissues involved in the glucose and hormonal compartments can be modified using sliding control displays.

In the HOMA2 model, insulin sensitivity is treated as a whole-body effect, altering the liver and periphery to the same extent. In iHOMA2, this has been uncoupled and the insulin sensitivity of these organs and tissues can be modified independently. The ability to alter the 24 variables of iHOMA2 enables the modeling of known or surmised pathology and physiology and the effect of treatments both alone and in combination. The effects of the treatments on fasting glucose, insulin, $b$-cell function (%B), and insulin sensitivity (%S) are graphically represented in the model.

The model allows for analytical and predictive modes of use. The analytical mode allows insulin resistance and $b$-cell function to be read from the input of insulin and glucose in the basal state, while
Liver Periphery (muscle, fat)
a measure of insulin resistance (IR) sometimes used instead. So %S=50% is the same as IR=2.

Percentage of normal (100%) beta cell function. %S is the percentage of normal (100%) sensitivity. 100/%S gives

Table 1—Modifiable variables within iHOMA2

| Name      | Description                                                                 |
|-----------|-----------------------------------------------------------------------------|
| \( P_1 \) | %-B Cell function of the islets                                              |
| \( P_2 \) | Max Maximum output of insulin                                               |
| \( P_3 \) | Effective concentration Glucose concentration required before insulin release started |
| \( P_4 \) | Slope factor (Hill slope) Rate of insulin secretion modifier 1              |
| \( P_5 \) | Hyperbolic/sigmoid operator Rate of insulin secretion modifier 2            |
| Liver     | \( L_1 \) Intercept Initial glucose output                                   |
|           | \( L_2 \) Insulin effect Insulin concentration effect                       |
|           | \( L_3 \) Max Maximum glucose output                                        |
|           | \( L_4 \) Slope Rate of glucose output                                      |
|           | \( L_5 \) %-S Sensitivity of glucose output to insulin                      |
| Periphery (muscle, fat) | \( PE_1 \) Max Maximum glucose uptake                                      |
|           | \( PE_2 \) Slope A Primary rate of glucose uptake                            |
|           | \( PE_3 \) Slope B Secondary rate of glucose uptake                          |
|           | \( PE_4 \) Insulin effect Insulin concentration effect                      |
|           | \( PE_5 \) %-S Sensitivity of glucose uptake to insulin                      |
| Gut       | \( G_1 \) Max Maximum glucose uptake                                         |
|           | \( G_2 \) Slope Rate of glucose uptake                                       |
| Brain     | \( B_1 \) Max Maximum glucose uptake                                         |
|           | \( B_2 \) Slope Rate of glucose uptake                                       |
| Renal     | \( R_1 \) Slope A Primary rate of glucose excretion                         |
|           | \( R_2 \) Slope B Secondary rate of glucose excretion                       |
|           | \( R_3 \) Delay Glucose concentration required before glucose excretion started |
|           | \( R_4 \) Threshold Glucose concentration basal threshold                   |

The iHOMA2 variables that can be modified by the operator either by using a sliding scale on the interface or by entering exact values. The absolute values at default are equal to those used in HOMA2. %-B is the percentage of normal (100%) beta cell function. %-S is the percentage of normal (100%) sensitivity. 100/%-S gives a measure of insulin resistance (IR) sometimes used instead. So %S=50% is the same as IR=2.

Quantitative model usage: effect of pioglitazone
To model the effects of pioglitazone, we examined the outcome when insulin sensitivity was modeled to be in the liver, in the periphery, or at both sites equally—all with a standardized increase in \( \beta \)-cell function. Three possible sites of action on insulin sensitivity for pioglitazone were modeled: hypothesis 1, insulin sensitivity increases in both periphery and hepatic (variables \( L_5 \) and \( PE_3 \)); hypothesis 2, hepatic insulin sensitivity increases and peripheral insulin sensitivity remains unchanged (variable \( L_5 \)); and hypothesis 3, hepatic insulin sensitivity remains unchanged and peripheral insulin sensitivity increases (variable \( PE_3 \)).

The development dataset comprised insulin and glucose values from a monotherapy study of pioglitazone (16). The changes to \( \beta \)-cell function and insulin sensitivity observed between the baseline visit and end of study (12 months later) in the development group were used as inputs to adjust the variables in the iHOMA2 model for each of the three hypotheses. A separate study of pioglitazone (17) was used for the verification group. The data from the baseline visits of the verification group were submitted to the adjusted iHOMA2, using the model in predictive mode, to determine the effect of pioglitazone for each of the three hypotheses using as output the expected fasting glucose and insulin after therapy. We assessed bias and agreement using a Bland-Altman plot and assessed the fit of the model by examination of the least squares deviation from the line of unity (where the observed values equal the predicted values) using an F statistic to test the model fit.

Quantitative model usage: effect of glucose reabsorption inhibitors
SGLT2 partially prevent the reabsorption of glucose, thus changing the renal threshold for glycosuria. Patients using an SGLT2 inhibitor demonstrate a marked increase in glucose urinary loss. A recent publication estimated, for a 5-mg dose of dapagliflozin over 2 weeks, a 20% decrease in the renal threshold for glycosuria (18). To model the effect of SGLT2 inhibition, we used a phenotypically similar subject set (previously published [19]) where fasting glucose and insulin measurements were known. SGLT2 inhibition was modeled in iHOMA2 (variable \( R_4 \) = 120%) based on the published data to predict the effect on the fasting glucose and insulin. The glucose changes predicted were compared with a separate preselected phase 3 trial of dapagliflozin (20) using an independent \( t \) test.

Further, the iHOMA2 model was used to examine any change required in renal glucose excretion to achieve an equivalent change in fasting glucose in our cohort. iHOMA2 was manipulated (by change of variable \( R_4 \)) until the change in glucose from the model was equal to the change in glucose from the dapagliflozin study. The value of the variable \( R_4 \) was then read from the model.

RESULTS
Quantitative model usage: effect of pioglitazone
Data were analyzed for normal distribution before parametric analysis. The \( z \) test
value for the skewness of the insulin data was 3.9. Log transformation eliminated the skewness as indicated by the z value of 0.5. Geometric mean insulin results are therefore presented.

In the development group, pioglitazone increased β-cell function from 36.9 to 49.2, a relative increase of 33.4%, and increased insulin sensitivity from 61.4 to 79.3, a relative increase of 29.1%. Since we now had a calculated generic change in insulin sensitivity with an associated β-cell functional change, we were able to partition the site of resistance to test three hypotheses (Fig. 2):

1. That insulin resistance change with pioglitazone is equally partitioned between the liver and the periphery. Whence we set hepatic insulin sensitivity increase by 29.1% with β-cell function increased by 33.4% (variables $L_5 = 129.1\%$, $PE_5 = 129.1\%$, $P_1 = 133.4\%$).

2. That insulin resistance change with pioglitazone is only sited at the liver. Whence we set hepatic insulin sensitivity increase by 58.2%, peripheral insulin sensitivity unchanged, and β-cell function increase by 33.4% (variables $L_5 = 100.0\%$, $PE_5 = 158.2\%$, $P_1 = 133.4\%$).

3. That insulin resistance change with pioglitazone is only sited at the periphery. Whence we set peripheral insulin sensitivity increase by 58.2%, hepatic insulin sensitivity unchanged, and β-cell function increase by 33.4% (variables $L_5 = 100.0\%$, $PE_5 = 158.2\%$, $P_1 = 133.4\%$).

The predicted change in glucose and the change in insulin from these hypotheses were contrasted with the observed values from the verification group using Bland-Altman plots and F tests for model fit. The Bland-Altman plots did not show significant differentiation between the models. F test (Table 2) demonstrated that the second hypothesis—maximal hepatic insulin sensitivity—was found to be the model with the best fit to the observed data. The F statistics for linearity were 139 and 259 (with 668 df) (significance $P < 0.001$) for glucose and insulin, respectively.

Quantitative model usage: the effect of glucose reabsorption inhibitors

iHOMA2 predicted that a decrease by 20% in the renal excretion threshold using 5 mg dapagliflozin treatment over 2 weeks would result in a decrease in mean (SD) glucose of 1.1 (0.3) mmol/L in the study subjects. Data extracted from published literature on dapagliflozin (5-mg dose) reported a similar change in mean glucose of 0.9 mmol/L in their subjects after 2 weeks. There was no significant difference between the model and the observed data. There are no published data on changes in insulin, so these could not be compared.

Although the model and observed results were broadly concordant, further manipulation of the iHOMA2 models renal excretion threshold variable ($R_4$) suggested that alteration of the renal threshold by 17% ($R_4 = 117\%$) gave the closest approximation for the observed mean decrease of 0.9 mmol/L in glucose.

CONCLUSIONS—iHOMA2 is an extension of HOMA2 that enables the interactive modeling of physiology and treatment effects. It is now possible to use more of the potential of the structural basis of the model through the 24 interactive variables. This circumvents a drawback of HOMA2, namely, that this model does not allow individual compartmental or biological variables to be

| Hypothesis | Pancreas | Liver | Periphery | Variables changed |
|------------|----------|-------|-----------|-------------------|
| No Change  | ![Pancreas](image1) ![Liver](image2) ![Periphery](image3) | $P_1 = 100.0$ $PE_5 = 100.0$ $L_5 = 100.0$ |
| Hypothesis 1— Increases beta cell function by 33.4%, peripheral insulin sensitivity by 29.1% and liver sensitivity by 29.1% | ![Pancreas](image4) ![Liver](image5) ![Periphery](image6) | $P_1 = 133.4$ $PE_5 = 129.1$ $L_5 = 129.1$ |
| Hypothesis 2— Increases beta cell function by 33.4%, peripheral insulin sensitivity by 0% and liver sensitivity by 58.2% | ![Pancreas](image7) ![Liver](image8) ![Periphery](image9) | $P_1 = 133.4$ $PE_5 = 158.2$ $L_5 = 158.2$ |
| Hypothesis 3— Increases beta cell function by 33.4%, peripheral insulin sensitivity by 58.2% and liver sensitivity by 0% | ![Pancreas](image10) ![Liver](image11) ![Periphery](image12) | $P_1 = 133.4$ $PE_5 = 158.2$ $L_5 = 100.0$ |
Table 2—Example of hypothesis predictions from the iHOMA2 model

| Insulin sensitivity | Mean Δglucose (mmol/L) Observed Modeled F  | Geometric mean Δinsulin (pmol/L) Observed Modeled F  |
|---------------------|-------------------------------------------|-------------------------------------------------|
| Hypothesis 1: 50% hepatic, 50% peripheral | -2.4 -2.7 143* | -8.2 -14.6 970* |
| Hypothesis 2: 100% hepatic | -2.4 -2.6 139* | -8.2 -11.5 259* |
| Hypothesis 3: 100% peripheral | -2.4 -2.9 141* | -8.2 21.4 650* |

Example 1: Modeling drug effects (pioglitazone). Change in mean glucose and insulin predicted by the iHOMA2 model compared with observed results from an independent study using the F statistic to test model fit. *Significant to P < 0.001.

Mathematical models, such as the Mari model (4) or Bergman minimal model (3), are useful for the study of complex phenomena, as they demonstrate how measurements of glucose and insulin can be seen as manifestations of a complex feedback process. iHOMA2 has the functionality to display the individual components of the glucose and insulin interaction and resolve the steady-state mathematics to yield measures of β-cell function and insulin resistance. Using the model interactively, one can predict (and display graphically) many pathological and physiological scenarios. iHOMA2 can also be individualized, by adjustment of the variables, to specific phenotypes, genotypes, populations, or individuals.

The iHOMA2 model does have the disadvantage in that, in common with all mathematical models, it has limitations to its use and is not intended to provide a "complete" metabolic description. Allowing many variables to be internally manipulated means that identifiability of a solution can be at risk (its identifiability is reduced). So, iHOMA2 records a list of the 24 variables currently able to be changed and their settings. For transparency in reporting, we would advise that the values of the settings on the model are explicitly stated when they differ from the default. iHOMA2 is still a homeostatic model; i.e., it calculates a steady-state solution. The HOMA2 model was expanded to include glucose infusion kinetics (27). Further work is underway in iHOMA2 to add dynamic aspects so that glucose tolerance tests or clamp data could be modeled. A drawback of iHOMA2 is that it loses the simple assessment aspect of HOMA2—where there are two outputs from two inputs. iHOMA2 is, instead, a more user-definable model allowing the individual characteristics of organs and tissues to be manipulated. This manipulation allows for hypothesis testing of treatment effects and the modeling of pharmaceutical treatments for clinical care.

In conclusion, the creation of the iHOMA2 model addresses some of the limitations with our previous invariant model. iHOMA2 is an application for extending the range of the existing HOMA2 model and can be used to evaluate therapeutic agents in greater physiological detail and can predict their effects on fasting glucose and insulin and on β-cell function and insulin sensitivity. iHOMA2 can be used for hypothesis testing, for the evaluation of pharmaceutical
iHOMA2: an interactive HOMA model

agents, for the estimation of effect sizes of therapies, and for evaluation of indicative changes to glucose when a combination of agents is used. It can be used in its default mode to generate HOMA2 results directly comparable with those in the literature. The iHOMA2 program is freely available (http://www.ihoma.co.uk) for academic and noncommercial use.

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N.R.H. researched data, wrote the manuscript, and coded the iHOMA2 program. J.C.L. and D.R.M. provided intellectual input into the modeling, wrote parts of the paper and discussion, and reviewed and edited manuscript. D.R.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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