Evaluation of a Glomerular Filtration Term in the DISST Model to Capture the Glucose Pharmacodynamics of an Insulin-Resistant Cohort.

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Abstract: Glomerular filtration (kidney clearance) of glucose occurs at high glucose concentrations. Thus, the applicability of glomerular filtration terms in models of insulin and glucose pharmaco-dynamics (PD) should be investigated.

To evaluate such a term, data from 36 insulin sensitivity tests on 12 participants with type 2 diabetes in an Atkins diet intervention study was analysed using three PD models. The models include the dynamic insulin sensitivity and secretion test (DISST) model the DISST model with an added glomerular filtration rate (GFR) term and the well-known Minimal Model (MM). The identified insulin sensitivity values and simulation fit-to-data residuals are analysed to test performance and differences.

The Minimal Model produced the best fit-to-data with a median residual of 0mmol/L and IQR of -0.13, 0.18mmol/L. Both DISST models also produced residuals with a median of 0mmol/L but an IQR of approximately -0.41, 0.37mmol/L. However, the DISST derived sensitivity values were considerably more in accordance with expected trends, showing the expected 20-50% increase in sensitivity for most subjects due to the intervention. In contrast, the Minimal Model repeated the variable trade-off issue previously recorded for this model with insulin resistant participants. The Minimal Model sensitivity values were effectively random, and did not capture observable changes in insulin sensitivity of glucose clearance.

The addition of a GFR term had a positive impact on the identified insulin sensitivity by shifting some values more toward expected and observable behaviour. However, more data must be made available for an exhaustive investigation of the applicability of this term for this type of usage.

Keywords: Physiological Modeling, pharmaco-kinetics/dynamics, parameter identification, glomerular filtration, insulin sensitivity.

1. INTRODUCTION

The dynamic insulin sensitivity and secretion test (DISST) model was developed to define the insulin and glucose pharmaco- kinetics (PK) and -dynamics (PD) during a relatively low-dose, short-duration insulin-modified intra-venous glucose tolerance test (IM-IVGTT) (Chase et al. 2006, Lotz 2007, Lotz et al. 2008, Lotz et al. 2010). In contrast to the Minimal Model of insulin and glucose PK-PD (Bergman et al. 1979), the DISST model utilises a single metric (insulin sensitivity (*SI*)) to model glucose decay. Although the two-metric Minimal Model could potentially provide additional information about a test participant's physiology, parameter interference and trade-off often occurs during identification as a result of assay error (Cobelli et al. 1998, Pillonetto et al. 2002, Quon et al. 1994). Bayesian techniques or a modified model can partially mitigate this issue (Cobelli et al. 1999, Denti et al. 2009, Erichsen et al. 2004, Pillonetto et al. 2003).

This article compares the simple Minimal Model against the existing DISST model and a modified DISST model that includes a term for glomerular filtration (kidney clearance of glucose) which occurs at high glucose concentrations (Arleth et al. 2000, Rave et al. 2006). The added glomerular filtration term used here is derived from the model of (Arleth et al. 2000). The models are presented in Equations (1)-(7):

DISST model:

$$\dot{Q} = \frac{n_I}{V_Q} I - (n_C + \frac{n_I}{V_Q}) Q \tag{1}$$

$$Q = e^{-\int n_C + \frac{n_I}{V_Q} dt} \left[Q_0 + \frac{n_I}{V_Q} \int e^{\int n_C + \frac{n_I}{V_Q} dt} I \, dt \right] \tag{1a}$$

$$\dot{G} = p_G (G_0 - G) - SI_{DISST} (GQ - G_0 Q_0) + \frac{P_X}{V_G} \tag{2}$$

$$G = e^{-\int p_G + SIQ dt} \left[G_0 + \int e^{-\int p_G + SIQ dt} \left(p_G G_0 + SIG_0 Q_0 + \frac{P_X}{V_G} \right) dt \right] \tag{2a}$$

Glomerular filtration DISST model:

$$\dot{G} = p_G(G_0 - G) - SI_{GFR}(GQ - G_0Q_0) + \frac{P_X - GFR \cdot BW}{V_G} \quad (3)$$

$$GFR = \begin{matrix} 0, & G < 10 \\ 0.077G^2 - 1.54G + 7.72 & 10 < G < 22 \\ 1.85G - 29.62 & G > 22 \end{matrix} \quad (4)$$

The glomerular filtration model uses Equation (1) to model insulin PKs.

Minimal Model:

$$\dot{X} = p_3(I - I_0) - p_2X \quad (5)$$

$$X = e^{-\int p_2 dt}\left[\int e^{\int p_2 dt} p_3(I - I_0)dt\right] \quad (5a)$$

$$\dot{G} = p_1(G_0 - G) - GX + \frac{P_X}{V_G} \quad (6)$$

$$G = e^{-\int p_1 + X dt}\left[G_0 + \int e^{\int p_1 + X dt}\left(p_1G_0 + \frac{P_X}{V_G}\right)dt\right] \quad (6a)$$

$$SI_{MM} = \frac{p_3}{p_2} \quad \text{and} \quad SG_{MM} = p_1 \quad (7)$$

where: equation nomenclature is defined in Table 1

Sym'	Description	Units
Q	Insulin concentration in the interstitium	mU/L
I	Insulin concentration in the plasma	mU/L
n_I	Rate of insulin transfer between interstitium and plasma	L/min
n_C	Rate of insulin uptake to cells	1/min
V_Q	Distribution volume of interstitial insulin	L
V_G	Distribution volume of glucose (variable)	L
G	Glucose concentration	mmol/L
p_G	Glucose dependant rate of glucose clearance	1/min
SI_{DISST}	Insulin sensitivity measured by the DISST model (variable)	L/mU/min
GFR	Glomerular filtration rate	mmol/L/min
SI_{GFR}	Insulin sensitivity measured by the modified DISST model (variable)	L/mU/min
P_X	Glucose bolus or infusion	mmol
X	Insulin action	1/min
p_1	Minimal Model rate variable	1/min,
p_2	Minimal Model rate variable	1/min,
p_3	Minimal Model rate variable	L/mU/min^2
SI_{MM}	Minimal Model insulin sensitivity (dependant on p_2-p_3)	L/mU/min
SG_{MM}	Glucose dependant rate of glucose clearance (dependant on p_1)	1/min

Table 1. Nomenclature from Equations (1)-(7)

2. METHOD

2.1 Study design

An intervention investigation evaluated the effect of the Atkins diet in a cohort of overweight and insulin resistant individuals with established type 2 diabetes with a series of physiological measurements and insulin sensitivity tests. Baseline characteristics were obtained prior to the commencement of the diet. The Atkins diet was prescribed as per the "Atkins Diet Revolution" book over 12 weeks. Weeks 12 to 24 involved a maintenance period during which time the goal was weight stability. Insulin sensitivity tests were undertaken at weeks 0, 12 and 24.

This research was approved by the New Zealand Ministry of Health, central regional ethics committee.

2.2 Participants

Fourteen individuals were recruited from the Wellington region of New Zealand to take part in the study. Inclusion criteria required that subjects had established type 2 diabetes and were aged between 30 and 65 years with a BMI between 27 and 40 kg/m^2. Participants were excluded if they had any major physiological or psychological illness at the time of testing, or were pregnant or lactating. During the study two subjects were omitted from the investigation (with one citing personal problems and the other exacerbating a renal stone.)

2.3 Test protocol

The insulin sensitivity test used in this study was defined in (Ward et al. 2001), but is repeated here for clarity:

A two-minute glucose infusion was began at t=0. The glucose infusion had a total glucose content of 0.2g/kg of participant bodyweight. An insulin infusion was started at t=2 minutes at a rate of 3.5mU/kg/min and was reduced to 0.5mU/kg/min at t=7 minutes. Further reductions occurred at t=17 minutes, to 0.25mU/kg/min, and at t=50 minutes, to 0.1mU/kg/min. The infusion of 0.1mU/kg/min was maintained for the remainder of the test. This insulin profile was selected to mimic the first and second insulin production phases of healthy, normo-glucose tolerant individuals. Blood samples were taken at times: t=-10, -5, -1, 0, 1, 2, 3, 4, 5, 6, 8, 10, 12.5, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 210, 240, 270, 300 minutes, and assayed for insulin and glucose.

2.4 Model identification methods

All model variables were identified using the iterative integral method (Docherty et al. 2009, Hann et al. 2005), which is briefly described below for the DISST, with extensions for the GFR and Minimal Models. As the models tested all use single compartment representations of insulin-glucose PDs, the data immediately after the glucose bolus will be discarded. The glucose concentrations in this period are an artefact of slow mixing, and although this can be modelled by two-compartment models, the resulting kinetic metrics are of little clinical relevance or value. Thus, this study will ignore glucose data between 0 and 10 minutes.

2.4.1 DISST model identification:

Initially, an approximation of the plasma insulin concentration is made by using a linear interpolation of the frequently-sampled plasma insulin data. This is used in Equation (1a) to simulate interstitial insulin.

Equation (2) is integrated and separated into the coefficients of the variables:

$$\begin{aligned} C_n &= G(n) - G_0 + p_G \int_0^n G - G_0 \, dt \\ S_n &= -\int_0^n GQ - G_0 Q_0 \, dt \\ V_n &= \int_0^n P_X \, dt \end{aligned} \tag{8}$$

Equation (8) is evaluated for each coefficient at each of the sample times except for the data between t=1 and 8 inclusive (n=-10, -5, -1, 0, 10, 12.5, …, 360) using a linear interpolation of the glucose data. This manipulation allows a matrix equation to be formulated:

$$\begin{bmatrix} S_{-10} & V_{-10} \\ S_{-5} & V_{-5} \\ S_{-1} & V_{-1} \\ \vdots & \vdots \\ S_{360} & V_{360} \end{bmatrix} \begin{bmatrix} SI \\ 1/V_G \end{bmatrix} = \begin{bmatrix} C_{-10} \\ C_{-5} \\ C_{-1} \\ \vdots \\ C_{360} \end{bmatrix} \tag{9}$$

SI and $1/V_G$ are identified using linear least squares and $G(t)$ is re-simulated using Equation (2) with these values. This enables an improved evaluation of the coefficients of Equation (8) and re-identification of *SI* and V_G. The process of re-simulating $G(t)$ and re-identifying *SI* and V_G is iterated 5 times, by which time variable convergence is generally on the order of 0.1%.

2.4.2 DISST with glomerular filtration model identification

The incorporation of GFR alters the DISST identification method very little. A *GFR* profile is evaluated for the duration of the test using the most recent glucose estimation and Equation (4). Initially, an interpolation of the glucose measurements is used, then the refined glucose concentration simulations are used. Equation (8) is thus modified as follows:

$$\begin{aligned} C_n &= G(n) - G_0 + p_G \int_0^n G - G_0 + \int_0^n GFR \\ S_n &= -\int_0^n GQ - G_0 Q_0 \\ V_n &= \int_0^n P_X \end{aligned} \tag{10}$$

The coefficients of Equation (10) are used in Equation (9) to identify *SI* and V_G and continue the iterative process as described in Section 2.4.1.

2.4.3 Minimal Model identification

The governing equations of the Minimal Model are rearranged to enable identification with the iterative integral method. Equation (5) can be rearranged and substituted into Equation (6) yielding:

$$X = X_0 + p_3 \int (I - I_0) \, dt - p_2 \int X \, dt \tag{11}$$

$$\dot{G} = p_1(G_0 - G) - G p_3 \int (I - I_0) \, dt + G p_2 \int (X) dt + \frac{P_X}{V_G} \tag{12}$$

Equation (12) can be integrated and evaluated for the coefficients of the variables at the sample times:

$$\begin{aligned} C_n &= G_n - G_0 \\ P1_n &= \int_0^n G_0 - G \, dt \\ P2_n &= \int_0^n \left[G \int_0^n X dt \right] dt \\ P3_n &= -\int_0^n \left[G \int_0^n (I - I_0) dt \right] dt \\ V_n &= \int_0^n P_X \, dt \end{aligned} \tag{13}$$

Again, a matrix equation is evaluated for the variables:

$$\begin{bmatrix} P1_{-10} & P2_{-10} & P3_{-10} & V_{-10} \\ P1_{-5} & P2_{-5} & P3_{-5} & V_{-5} \\ P1_{-1} & P2_{-1} & P3_{-1} & V_{-1} \\ \vdots & \vdots & \vdots & \vdots \\ P1_{360} & P2_{360} & P3_{360} & V_{360} \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \\ p_3 \\ 1/V_G \end{bmatrix} = \begin{bmatrix} C_{-10} \\ C_{-5} \\ C_{-1} \\ \vdots \\ C_{360} \end{bmatrix} \tag{14}$$

The Minimal Model contrasts from the DISST model in that the form of the $X(t)$ profile depends on the form of the $G(t)$ profile and must be re-evaluated (with Equation 5a) at each iteration. As such, parameter stability is not assured, and care must be taken to ensure parameter convergence. To ensure convergence, the change allowed in the identified variables is limited to 20% per iteration.

2.5 Evaluation methods

The identified variables from the three models will be presented and their ability to measure the clinical outcomes of the trials will be evaluated over the cohort and for individual cases. Furthermore, the median and inter-quartile range (IQR) of the residuals will be presented. The residual calculations will not include data omitted by the identification methods.

As the DISST model was designed for short duration tests, wherein counter-regulatory effects have minimal influence on the identified results, both the full data sets and an abbreviated version are used. The full data set uses data between t=-10 and t=360 minutes, while the shortened set will only use data between t=-10 and t=60 minutes. Both data sets exclude the glucose data between 1 and 8 minutes.

3. RESULTS

The models analysed produced the residuals shown in Figure 1 and summarised in Table 2. Figure 2 shows the raw data and simulated glucose profiles from the three sensitivity tests from an indicative cohort subject (Subject 3).

The abbreviated data set analysis produced the lowest residual error for each model tested. Thus, the insulin sensitivity values identified in this analysis are presented in Table 3 with basal glucose. The basal glucose allows an indication of the expected shift in insulin sensitivity.

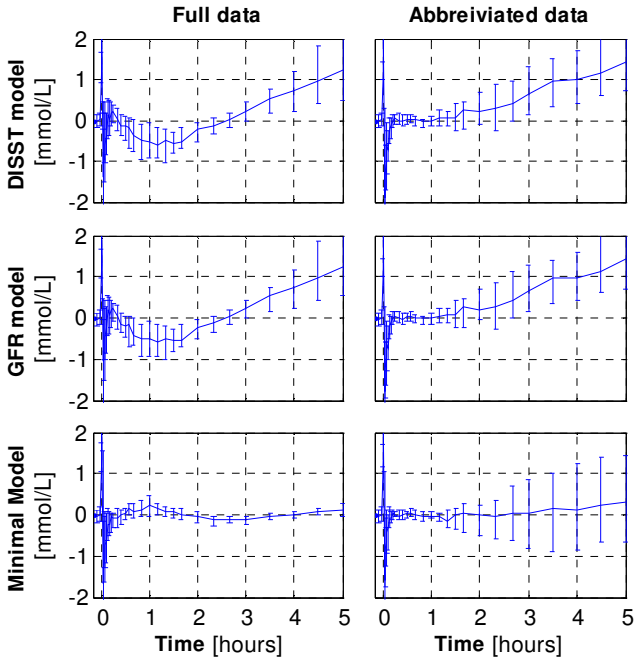

Figure 1. Residual plots from the three models using both full and abbreviated data sets.

Model	Full data residuals Median (IQR)	Abbr. data residuals Median (IQR)	Abbr. data full residuals Median(IQR)
DISST	0 (-0.412, 0.385)	0 (-0.115, 0.149)	0.075 (-0.102, 0.500)
GFR	0 (-0.415, 0.368)	0 (-0.112, 0.146)	0.077 (-0.095, 0.511)
MM	0 (-0.130, 0.180)	0 (-0.100, 0.122)	0 (-0.188, 0.226)

Table 2. Residuals of the simulated glucose profiles compared to the measured data [mmol/L].

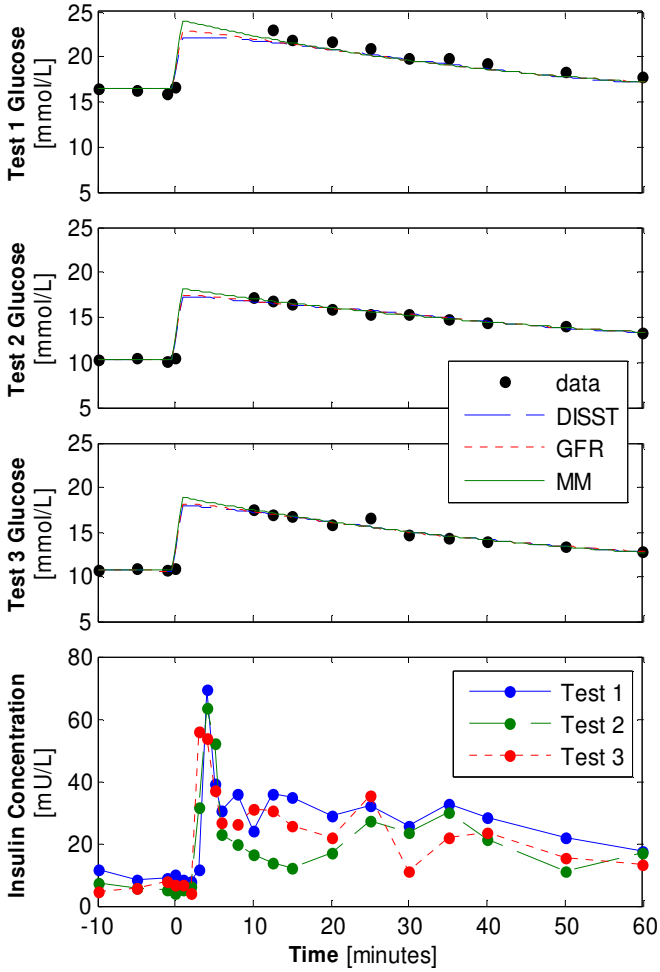

Figure 2. Raw data, simulated glucose profiles and plasma insulin concentrations from the three insulin sensitivity tests of Subject 3.

Subject	Basal Glucose [mmol/L] test 1	test 2	test 3	DISST test 1	test 2	test 3	DISST + GFR test 1	test 2	test 3	Minimal Model test 1	test 2	test 3
1	16.9	11.4	11.7	4.61	1.26	1.62	3.35	1.23	1.56	0.41	0	0
2	6.7	6.0	5.9	3.77	4.35	5.31	3.77	4.35	5.31	0.16	0.33	0.34
3	16.3	10.3	10.8	5.65	5.90	6.16	3.42	5.23	5.63	0.61	0	0.07
4	7.7	6.6	6.7	5.46	7.77	11.46	5.46	7.77	11.46	6.67	3.33	0.00
5	8.5	6.7	7.6	5.78	6.09	5.58	5.78	6.09	5.58	3.45	0.38	1.63
6	7.5	7.1	6.7	2.30	3.07	3.13	2.30	3.07	3.13	0	10.92	0.02
7	14.4	12.6	10.0	3.46	4.83	6.32	3.02	4.63	6.25	0.75	0.96	0
8	6.6	6.5	6.8	13.64	15.01	12.36	13.64	15.01	12.36	14.10	9.86	18.27
9	9.1	5.1	6.1	1.61	3.41	4.99	1.61	3.41	4.99	0	0.22	0.02
10	6.6	5.6	9.9	3.59	8.09	2.98	3.59	8.09	2.92	0.05	13.53	1.41
11	7.2	7.0	6.4	5.72	5.41	10.10	5.72	5.41	10.10	0.34	2.58	0.06
12	8.6	6.6	7.2	3.44	7.97	5.15	3.44	7.97	5.15	0.32	17.41	4.44

Table 3. Basal glucose and insulin sensitivity values identified using test data between t=-10 and 60 minutes [L/mU/min].

4. DISCUSSION

The residuals shown in Figure 1 and Table 2 show that the Minimal-Model enabled greater adherence to the measured data than the DISST models. This is an artefact of the contrasting modelling approaches. The Minimal Model uses four variables to model glucose that are known to trade-off during identification (Caumo et al. 1996, Pillonetto et al. 2002, Quon et al. 1994). Thus, the accuracy of the physiological variables is reduced for the benefit of improved data-fitting. In contrast, the DISST model uses two variables that produce poorer residuals, but yield more stable and relevant diagnostic clinical metrics.

Insulin sensitivity values from the models further confirmed this contrast in modelling strategies. The Minimal Model encountered the same parameter estimation issues published previously, and showed very poor continuity in sensitivity between trials for the study subjects. It is clear that variable trade-off occurred in this cohort for whom the Minimal Model has known problems (Quon et al. 1994).

In particular, the results of Subject 3 (Figure 3) highlight the different behaviours of the three models. Although there is very little shift in the insulin profiles across the three tests, there is an improvement in the rate of glucose decay. Furthermore, the basal glucose concentration was reduced considerably after the first test, indicating a significant improvement in this participants physiology. Although the standard DISST model captured an improvement, it was not of the magnitude expected. However, the addition of the GFR term produced more expected values. The Minimal Model insulin sensitivity values did not identify the expected trend, and it is obvious that parameter trade-off occurred during identification.

In contrast, the DISST models showed the expected increase in insulin sensitivity for most of the participating subjects. The exceptions were Subject 1 who had a drastically improved basal glucose; Subject 8 who maintained a relatively high sensitivity throughout the study; and Subject 10 who misinterpreted the Atkins diet to allow deep-fried fish-and-chips, and the resultant insulin sensitivity value was somewhat expected!

The addition of the glomerular filtration term seems to be a sensible addition to the model. The term only affects the sensitivity values of subjects who have high fasting glucose concentrations. For example, the standard DISST model seems to have over-estimated the Trial 1 insulin sensitivity of Subject 1. Within this cohort, the term had a significant effect on the sensitivity values of Subjects 1, 3, and 7. The added GFR term seems to have shifted the sensitivity values in the expected direction in each case.

The available data is not sufficient for an exhaustive analysis of the applicability of the GFR term for this type of test. However, this analysis has shown that the un-expected insulin sensitivity values from some participants with elevated fasting glucose were shifted further toward expected behaviour with the incorporation of the GFR term.

The residuals shown in Figure 1 indicate that all of the models tested were not particularly suited to defining the PK/PDs of these individuals during the protocol used. The protocol included an insulin infusion designed to mimic that of healthy normo-glucose tolerant individuals. The infusion contained first phase, second phase and continuous infusions. In many cases, the continuous infusion reduced the subjects' glucose below their basal concentrations. Thus, the SG_{MM} and P_G terms would become positive, denoting increased glucose production, (both model terms drive glucose back toward basal concentrations). In reality, it seems as though the exogenous insulin infusion was allowing the subjects physiology to drive the glucose concentration toward a healthy range. It could be supposed that this contrast between 'basal' and 'set-point' glucose concentration for these insulin resistant subjects was the cause of the poor residual results of the DISST models and the variable trade-off presented by the Minimal Model.

This analysis has chosen to analyse the simple Minimal Model in the form it was presented by (Bergman et al. 1979). It is well known that there have been advances in the application of the Minimal Model, which include two-compartment glucose (Cobelli et al. 1998, Mari et al. 2003), and Bayesian techniques to ameliorate variable trade-off (Denti et al. 2009, Pillonetto et al. 2002). The two-compartment method was not used as the DISST model ignores the data immediately after the glucose bolus. (The assumption is that there is no relevant diagnostic information contained in this data.) Therefore, to allow a fair comparison, the single compartment Minimal Model is used. The Bayesian techniques reduce variable trade off, but 'borrow' information from isolated data sets. Thus, the resultant variable values are affected by the population results, and do not present a most accurate possible model simulation of the available data.

5. CONCLUSIONS

Predominantly, this analysis has shown that clinically relevant diagnoses are not necessarily achievable through accurate residuals, but through useful metrics and the avoidance of including too many variables in a model. Although the Minimal Model residuals were considerably better than those of the DISST models, the resultant insulin sensitivity values of the Minimal Model were quite different from the expected behaviour. In contrast, both DISST models generally produced insulin sensitivity values in accordance with expected trends.

The added glomerular filtration term shifted some of the insulin sensitivity values of some subjects, and produced what would seem more reasonable outcomes. Although these findings are promising, more data must be made available for an exhaustive analysis of the applicability of the added term.

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