Evaluation of a glomerular filtration term in the DISST model to capture the glucose pharmacodynamics of an insulin resistant cohort

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Study design

Study: 24 week Atkins-diet based intervention

- Weeks 1-12 weight loss stage. Weeks 13-24 weight maintenance
- Significant carbohydrate limit ~20g/day – target energy composition: 20-25% via carbohydrate; 30% via protein; and 45-50% via fats

Participants: 12 individuals with established type 2 diabetes

- Duration of diabetes 0.5-12 years
- BMI range 34-46kg/m²
- Exclusion criteria: No other major illness or recent weight change

Study Evaluation

Tests: Week 0, 12 and 24

- Bodyweight and composition
- Fasting assays – lipids, HbA1c, Creatinine
- Insulin sensitivity (SI) test

SI test protocol: GM Ward et al. (Metabolism 2001 50(5))

- 0.2g/kg Glucose bolus (t=0)
- $3.5\text{mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ insulin (0 to 2); $0.5\text{mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (7 to 17); $0.25\text{mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (17 to 50) $0.1\text{mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (50 to 300)
- 33 samples, 5+ hours - Samples at 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
- Assayed for glucose and insulin

S/ test evaluation

Model Based:

- Standard DISST model (McAuley et al. 2011 Metabolism)
- DISST model modified with a glomerular filtration (GFR) term
- DISTq (Docherty et al. 2009 Open Med. Inf. J. 3)
- Minimal Model

Simple Measures:

- Area Under the Curve (AUC) glucose (AUC_G), and insulin (AUC_I)
- HOMA
- Basal assays: glucose (G_B), insulin (I_B), HbA1c and triglyceride (TAG)

DISST model

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

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

DISST validation

- Sparsely-sampled, low-dose, short duration IM-IVGTT protocol
- Concurrent model-based assessment of SI and endogenous insulin production
- High intra-patient repeatability (11-13% variation)
- High gold standard correlation ($R=0.81$), absolute ($\Delta_{\text{median}}=-10.6\%$) and diagnostic equivalence (ROC c-unit=0.96)

Important note: DISST protocol was not undertaken

→ results of this study not indicative of DISST test

Glomerular filtration term

From Arleth et al. (2000 CMPB 62(3))

- Initial trace of clearance at ~10 mmol/L glucose
- Linear clearance at ~22 mmol/L glucose
- Smooth transition

$$GFR = \begin{cases} 0, & G < 10 \\ 0.077G^2 - 1.54G + 7.72 & 10 < G < 22 \\ 1.85G - 29.62 & G > 22 \end{cases} / 1000$$

$$\dot{G} = p_G (G_0 - G) - SI_{DIST} (GQ - G_0 Q_0) + \frac{P_X - GFR \cdot BW}{V_G}$$

Parameter identification

The iterative integral method (IIM):

- Robust → not dependent on starting estimations
- Does not locate local minima
- Computationally quick → recent studies have exhibited a 3 to 350x faster convergence than Levenburg-Marquardt algorithms.
- Does not explicitly map error surface → does not become unstable due to over-sized convergence steps
- Docherty *et al.* published in application (Open Med. Inf. J 2009 3) - validation paper in review (Med. Biol. Eng. Comput.)

IIM method

1. Simulate species: G =interpolate G data
2. Evaluate eqn coefficients at sample times:

$$\text{LHS} = G_i - G_0 + p_G \int G(t) - G_0 dt_{0 \rightarrow i}$$

$$\text{CSI} = - \int G(t) Q(t) - G_0 Q_0 dt_{0 \rightarrow i}$$

$$\text{CV}_G = \int P_x(t) - \text{GFR}(t) * BW dt_{0 \rightarrow i} \quad \text{where } i \text{ is the sample times}$$

3. Evaluate matrix representation:

$$\{\text{LHS}_{0 \rightarrow i}\}^T = [\text{CSI}_{0 \rightarrow i}, \text{CV}_{G0 \rightarrow i}] \{SI, 1/V_G\}^T$$

4. Re-simulate $G(t)$ as function of SI and V_G outcomes, re-simulate $\text{GFR}(t)$ if relevant
5. Repeat steps 2 to 4 until convergence

Minimal Model ID

Minimal model is re-arranged to allow identification with IIM:

- Governing eqns: $\dot{G} = p_1(G_0 - G) - GX + \frac{P_X}{V_G}$

$$\dot{X} = p_3(I - I_0) - p_2X, \quad SG_{MM} = p_1, \quad SI_{MM} = p_3/p_2$$

- Can be rearranged: $X = X_0 + p_3 \int (I - I_0) dt - p_2 \int X dt$

$$\dot{G} = p_1(G_0 - G) - Gp_3 \int (I - I_0) dt + Gp_2 \int (X) dt + \frac{P_X}{V_G}$$

$$G - G_0 = p_1 \int (G_0 - G) dt - p_3 \int G \int (I - I_0) d\tau dt + p_2 \int G \int (X) d\tau dt + \frac{1}{V_G} \int P_X dt$$

- And enable the matrix formulation using the following

Coefficients: LHS; $C_n = G_n - G_0$, RHS; $P1_n = \int_0^n G_0 - G dt$,
 $P2_n = \int_0^n G \int_0^n X d\tau dt$, $P3_n = - \int_0^n G \int_0^n (I - I_0) d\tau dt$ and $V_n = \int_0^n P_X dt$

Comparison of IIM and Levenberg-Marquardt (L-M)

(Minimal model identified using full dataset in IIM and L-M parameter identification methods)

- Residuals of IIM comparable to L-M
- L-M much faster than IIM due to indirect identification of parameters in IIM
- Not ideal application of IIM – but it worked nonetheless!

Comparison between DISST, DISST+GFR and Minimal model

MM vs DISST
insulin sensitivity

DISST+GFR vs DISST
insulin sensitivity

- Minimal model SI was very different to DISST SI
- DISST SI very similar to DISST+GFR SI

Residuals

- Minimal model solutions were generally more adherent to the measured data
- DISST and DISST+GFR were not able to characterise 300 minute profile, but were similar to MM over -10 to 60mins

Investigation outcomes

- Compliance to the conditions of the dietary intervention trial was *generally* good
- Weight loss was observed across the trial

Model-based outcomes

- Minimal model parameter identification frequently reached bounds → unusable results
- DISST measured realistic results
- DISST+GFR modulated range in more realistic direction
- DISTq failed to estimate insulin concentration, thus S_I accurately

Simple metric outcomes

- Fasting assays ($HbA1c$, G_B , I_B , TAG) generally improved
- ΔAUC_G was indistinct to ΔG_B ($\rho=0.90$) $\rightarrow$ obsolete
- ΔAUC_I was indistinct to ΔI_B ($\rho=0.69$) $\rightarrow$ obsolete
- $\Delta HOMA$ similar to ΔI_B ($\rho=0.94$)

Study outcomes

Regarding model-based metrics:

- Minimal model unstable in this IR cohort → previously reported
- DISST stable, but unable to characterise longer-term steady-state condition. DISTq stable – but inaccurate.
- Adding variable model parameters can aid residuals but can also obscure results or disable stable parameter estimation
- The addition of the GFR term modulated the glucose clearance in some IFG participants and had a positive contribution to the study outcomes. However the effect was too small to assess

Study outcomes

Regarding simple metrics:

- Simple, single blood-test HOMA observed very large, possibly excessive changes
- HbA1c, G_B , I_B and weight all exhibited positive outcomes at a cohort level
- ΔG_B described the same changes as $\Delta AUC_G \rightarrow$ clinical protocol was not necessary if AUC_G is intended
- ΔI_B described the same changes as $\Delta AUC_I \rightarrow$ clinical protocol was not necessary if AUC_I is intended
- TAG exhibited reasonable behaviour but had a significant number of confounders