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)
• 3.5mU·kg$^{-1}$·min$^{-1}$ insulin (0 to 2); 0.5mU·kg$^{-1}$·min$^{-1}$ (7 to 17); 0.25mU·kg$^{-1}$·min$^{-1}$ (17 to 50) 0.1mU·kg$^{-1}$·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
SI 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

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

\[
\dot{G} = p_G (G_0 - G) - SI_{DISST} (GQ - G_0 Q_0) + \frac{P_X - GFR \cdot BW}{V_G}
\]
Parameter identification

The iterative integral method (IIM):

- Robust $\rightarrow$ not dependent on starting estimations
- Does not locate local minima
- Computationally quick $\rightarrow$ recent studies have exhibited a 3 to 350x faster convergence than Levenburg-Marquardt algorithms.
- Does not explicitly map error surface $\rightarrow$ does not become unstable due to over-sized convergence steps
IIM method

1. Simulate species: \( G = \text{interpolate } G \) data

2. Evaluate eqn coefficients at sample times:

\[
\text{LHS} = G_i - G_0 + p_G \int G(t) - G_0 \, dt_{0 \rightarrow i}
\]
\[
\text{CSI} = -\int G(t)Q(t) - G_0Q_0 \, dt_{0 \rightarrow i}
\]
\[
\text{CV}_G = \int P_X(t) - GFR(t)\ast BW \, dt_{0 \rightarrow i}
\]

where \( i \) 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 \( GFR(t) \) 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: \[
X = X_0 + p_3 \int (I - I_0)dt - p_2 \int Xdt \\
\dot{G} = p_1(G_0 - G) - Gp_3 \int (I - I_0)dt + Gp_2 \int (X)dt + \frac{P_X}{V_G} \\
G - G_0 = p_1 \int (G_0 - G)dt - p_3 \int G \int (I - I_0)d\tau dt + p_2 \int G \int (X)d\tau dt + \frac{1}{V_G} \int P_X dt
\]

- 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)

- 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!

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

  - $\Delta$ AUC$_G$ was indistinct to $\Delta G_B$ ($\rho=0.90)$ → obsolete

  - $\Delta$AUC$_I$ was indistinct to $\Delta I_B$ ($\rho=0.69)$ → obsolete

  - $\Delta$HOMA similar to $\Delta I_B$ ($\rho=0.94)$
Study outcomes

Regarding model-based metrics:

- Minimal model unstable in this IR cohort \( \rightarrow \) 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

• $\Delta G_B$ described the same changes as $\Delta \text{AUC}_G \rightarrow$ clinical protocol was not necessary if $\text{AUC}_G$ is intended

• $\Delta I_B$ described the same changes as $\Delta \text{AUC}_I \rightarrow$ clinical protocol was not necessary if $\text{AUC}_I$ is intended

• TAG exhibited reasonable behaviour but had a significant number of confounders
Questions?