Clinical Validation of the Quick Dynamic Insulin Sensitivity Test

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***Abstract*—The quick dynamic insulin sensitivity test (DISTq) can yield an insulin sensitivity result immediately after a 30-min clinical protocol. The test uses intravenous boluses of 10 g glucose and 1 U insulin at $t = 1$ and 11 min, respectively, and measures glucose levels in samples taken at $t = 0$, 10, 20, and 30 min. The low clinical cost of the protocol is enabled via robust model formulation and a series of population-derived relationships that estimate insulin pharmacokinetics as a function of insulin sensitivity (*SI*). Fifty individuals underwent the gold standard euglycaemic clamp (EIC) and DISTq within an eight-day period.*SI* values from the EIC and two DISTq variants (four-sample DISTq and two-sample DISTq30) were compared with correlation, Bland–Altman and receiver operator curve analyses. DISTq and DISTq30 correlated well with the EIC [$R = 0.76$ and 0.75, and receiver operator curve c-index = 0.84 and 0.85, respectively]. The median differences between EIC and DISTq/DISTq30 *SI* values were 13% and 22%, respectively. The DISTq estimation method predicted individual insulin responses without specific insulin assays with relative accuracy and thus high equivalence to EIC *SI* values was achieved. DISTq produced very inexpensive, relatively accurate immediate results, and can thus enable a number of applications that are impossible with established *SI* tests.**

***Index Terms*—*A posteriori* parameter identification, insulin sensitivity, parameter identification, structural model identifiability.**

I. Introduction

INSULIN sensitivity (*SI*) is an important metabolic characteristic that can indicate the risk of developing type 2 diabetes, cardiovascular disease, and the metabolic syndrome [1]–[7]. Established insulin sensitivity tests are either low intensity and low accuracy, or high intensity with improved accuracy. *SI* can be measured *in vivo* using several different types of clinical tests [8], [9]. Dynamic tests that use bolus stimuli of glucose, and sometimes insulin, are often undertaken to yield data that are assessed for model-based metrics of insulin sensitivity. The minimal model of insulin/glucose pharmacodynamics has been used extensively to model patient responses to measured blood glucose and insulin samples [10]–[12]. However, the concurrent identification of *SI* and glucose sensitivity S_G terms in the minimal model becomes practically nonidentifiable [13], [14] in some clinically relevant cohorts [13], [15], [16], despite the theoretical structural identifiability of the model [17]–[19].

The limited practical identifiability of the model despite theoretical identifiability [13] has led to an increase in protocol duration and sampling frequency with the aim of gaining sufficient data to increase error surface convexity. Increased error surface convexity typically enables more effective parameter identification [20]. In some cases, protocol duration has extended up to 5 h [21], [22]. Bayesian methods have also been used to improve results, but limit the influence of the patient-specific response to the test stimulus in the identified value and negate the uniqueness of the identified model parameters. Furthermore, the sensitivity to glucose S_G term has a limited clinical value in comparison to the insulin sensitivity term [23], [24] and may obscure the strength of the patient-specific data signal [13], [14].

Prior work hypothesised that by setting the S_G term to a population constant [13], [25] and identifying *SI* only, model structural identifiability would be improved. Hence, protocol duration, clinical intensity, and cost could be reduced. Preliminary studies of the quick dynamic insulin sensitivity test (DISTq) have shown that fixing S_G could improve model identifiability to an extent that would eliminate the need for insulin and C-peptide assays [26]–[28]. Insulin and C-peptide assays account for a significant proportion of the clinical cost of the test, and are the only aspect of the protocol that cannot be undertaken at the bedside. Hence, if the findings of these preliminary studies were clinically validated, the DISTq could be proposed as a low-cost *SI* test with the unique ability to yield results immediately after the test.

In this investigation, DISTq *SI* values from 50 individuals are compared to *SI* values obtained by the gold standard euglycaemic clamp (EIC) method [8]. Two DISTq variants are tested: a four-sample DISTq and a version that only uses the initial and final glucose samples (DISTq30) [28].

II. Methods

Data for this study were gathered during the validation of the dynamic insulin sensitivity and secretion test (DISST) [29].

Manuscript received August 17, 2012; revised November 12, 2012; accepted November 13, 2012. Date of publication December 11, 2012; date of current version April 15, 2013. This work was supported in part by the New Zealand Health Research Council and the New Zealand Foundation for Research, Science and Technology. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2012.2232667

A. Participants

Fifty Participants (25 M/25 F) from the Canterbury region of New Zealand were recruited via newspaper advertisements and flyers posted on notice boards at Christchurch Hospital and Canterbury University. Ten lean [body mass index (BMI) $\leq$ 25], 20 overweight (25 $<$ BMI $\leq$ 30), and 20 obese (BMI $>$ 30) participants were recruited. Each category had an even gender distribution. The median BMI of the cohort was 28.6 kg·m^{-2} [inter-quartile range (IQR: 25.9–33.0, range: 19.0–64.9] and the median age was 41 (IQR: 29–49, range: 20–69).Participants were excluded if they had any major physical or psychological illness, including type 1 or type 2 diabetes. Approval for this study was granted by the Upper South Island Regional Ethics Committee B and all participants signed informed consent prior to any tests.

B. Clinical Test Protocols

Participants underwent EIC, DISST, and oral glucose tolerance test (OGTT) protocols within an eight day period in a randomized order. All tests began at 9 A.M. after a 12 h fast and were undertaken at the endocrine test centre of the Christchurch Hospital. Participants were weighed and had their height measured prior to their first test. All participants sat in a supine position for the duration of the tests.

1) Euglycemic Hyperinsulinaemic Clamp: The EIC was undertaken according to the method described by Ferrannini and Mari [8]. Insulin (actrapid, Novo Nordisk) and glucose (25% dextrose) were infused into the participant via a cannula in the antecubtial fossa. Insulin was infused at 40 mU·m^{-2}·min^{-1} to obtain a target plasma insulin concentration of 100 mU·L^{-1}. Blood samples were taken at 5 min intervals via a cannula that was placed retrograde in the dorsum of the hand. The participants hand was placed in a purpose-built heated hand box. Glucose levels in the samples were measured at the bedside to allow the clinician to maintain euglycaemia by modulating the glucose infusion rate. Samples at $t = 60$, 80, 100, and 120 min were assayed for insulin.

2) DISST: Participants had a catheter inserted in their antecubital fossa. A 10 g glucose bolus (50% dextrose) was administered via the catheter at $t = 1$ min and a 1 U insulin bolus (actrapid, Novo nordisk) was administered at $t = 11$ min. Blood was sampled from the catheter immediately before the glucose and insulin assays ($t = 0$, and 10 min), and at $t = 5$, 20, and 30 min. Blood concentrations of glucose, insulin, and C-peptide were measured. DISTq and DISTq30 did not use insulin or C-peptide data. The DISTq parameter identification method ignored the $t = 5$ min glucose measurement, and DISTq 30 ignored the $t = 5$, 9, and 20 min measurements.

3) OGTT: Participants drank a lightly carbonated drink with 75 g glucose content at $t = 1$ min. Blood samples obtained via a catheter in the antecubtial fossa were assayed for glucose and insulin at $t = 0$, 30, 60, and 120 min.

C. Assay Methods

Glucose was measured in whole blood using the YSI 2300 stat plus Glucose and L-Lactate analyzer (YSI incorporated, Yellow Springs, OH). Insulin and C-peptide levels were determined at Endolab, Canterbury Health Laboratories, via Roche Elecsys after polyethylene glycol (PEG) precipitation of immunoglobulins (Roche Diagnostics, Mannheim, Germany).

D. Parameter Identification

1) Euglycemic Hyperinsulinaemic Clamp: SI values from the EIC were calculated using an average of the glucose infusion rate over the final 40 min of the clamp protocol and the mean value of the plasma insulin measurements. A space correction term S_C was introduced to model any slight transients in the measured glucose during the final 40 min

$$ISI = \frac{100 \cdot \bar{P}_X}{\bar{I} \cdot B_W} + S_C \tag{1}$$

$$S_C = 0.864 \cdot \Delta G \tag{2}$$

where *ISI* is the EIC *SI* index (10^{-2} mg $\cdot$ L $\cdot$ (kg $\cdot$ pmol $\cdot$ min)$^{-1}$); $\bar{P}_X$ is the average glucose infusion rate over the final 40 min of the EIC (mg $\cdot$ min^{-1}); $\bar{I}$ is the mean plasma insulin level over the final 40 min of the EIC (pmol $\cdot$ L^{-1}); B_W is the subject's body weight (kg), and ΔG is the change in glucose across the final 40 min of the test (mmol $\cdot$ L^{-1}).

2) DISTq: DISTq uses glucose measurements from the DISST protocol, but not insulin or C-peptide measurements. This study examines a four-sample DISTq and a less clinically intense two-sample DISTq30 protocol. Insulin responses to test stimulus are estimated via a series of population-based relationships between *SI* and key insulin pharmacokinetic parameters. Hence, DISTq parameter identification requires a relatively computationally intense iterative *a posteriori* method. To make the method accessible to all groups, a stand-alone DISTq parameter identification program has been developed and is freely available upon request to the authors. Fig. 1 shows the DISTq parameter identification methodology.

Step 1: An arbitrary insulin sensitivity value is chosen to enable an initial estimation of the participant's insulin pharmacokinetic rate parameters. The identified insulin sensitivity value is not sensitive to the choice of starting value [26].

Step 2: Equations (3)–(7) define the relationships between the insulin sensitivity and insulin pharmacokinetic parameters. These equations were developed using an isolated cohort ($N = 46$) [25]. The isolated cohort was also from New Zealand and had a similar broad range of physiological characteristics to the 50 participants of this study (median BMI 25.5 kg $\cdot$ m^{-2}, IQR 24.0–33.4, range 19.5–41.3). Equations (3)–(7) were defined prior to the clinical study, and thus, the insulin and C-peptide measurements from this study had no influence on the DISTq pharmacokinetic estimates [29]:

$$n_L = 0.0924 + 0.0041(SI) \tag{3}$$

$$I_0 = 313.7(SI)^{-1.039} \tag{4}$$

$$U_{N,0} = 664.1(SI)^{-0.609} \tag{5}$$

$$U_{N,5} = 852.0(SI)^{-0.116} \tag{6}$$

$$U_{N,20} = 1658(SI)^{-0.892} \tag{7}$$

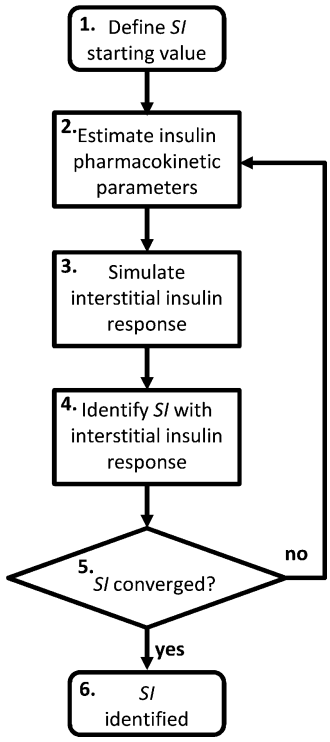

Fig. 1. Flowchart of the iterative *a posteriori* DISTq parameter identification process.

where n_L is the insulin clearance rate (min^{-1}), I_0 is the basal plasma insulin concentration ($\text{pmol} \cdot \text{L}^{-1}$), $U_{N,t}$ is the endogenous insulin production profile ($\text{pmol} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$), and insulin sensitivity is given in units of ($\times 10^{-4}$ $\text{mU} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$). Endogenous insulin is calculated at 1 min resolution in the algorithm, but is only shown here at $t = 0$, 5, and 20 for brevity.

Step 3: The insulin pharmacokinetic parameters defined in step 2 are used to simulate an interstitial insulin profile using

$$\dot{I} = -n_K I - n_L \frac{I}{1+\alpha_I I} - \frac{n_I}{V_P}(I-Q) + (1-x_L)\frac{U_N}{V_P} + \frac{U_X}{V_P} \tag{8}$$

$$\dot{Q} = \frac{n_I}{V_Q}(I-Q) - n_C Q \tag{9}$$

where n_K, n_I, and n_C, are rate parameters (min^{-1} or $\text{L} \cdot \text{min}^{-1}$, *a priori*); α_I is the saturation coefficient of liver clearance ($\text{L} \cdot \text{pmol}^{-1}$ *a priori*); I and Q are plasma and interstitial compartment insulin concentrations, respectively ($\text{pmol} \cdot \text{L}^{-1}$, simulated); U_X and P_X are the insulin and glucose bolus inputs, respectively ($\text{pmol} \cdot \text{min}^{-1}$ and $\text{mmol} \cdot \text{min}^{-1}$, respectively, *a priori*); V_P and V_Q are volumes of distribution (L, *a priori*); x_L is the fractional first pass liver extraction (dimensionless, *a priori*).

Step 4: The iterative integral method [30] is used to minimise the squared error between the measured glucose data and the glucose profile simulated by (10). The $t = 5$ glucose data point is not used due to potentially deleterious effects of unmodeled mixing. The interstitial insulin profile from Step 3 is used as model input. While DISTq identifies both *SI* and V_G as patient-specific model variables, DISTq30 identifies only *SI* and estimates V_G as 29% of lean body mass [28], [31].

$$\dot{G} = p_G(G_B - G) - SI(GQ - G_B Q_B) + \frac{P_X}{V_G} \tag{10}$$

where G is the glucose concentration in the plasma ($\text{mmol} \cdot \text{L}^{-1}$, simulated); p_G is a rate parameter (min^{-1}); V_G is the distribution volume of glucose (L, identified in DISTq, *a priori* in DISTq30); *SI* is the insulin sensitivity ($\text{L} \cdot \text{pmol}^{-1} \cdot \text{min}^{-1}$, identified); and G_B and Q_B are basal levels of each respective species.

Step 5: The *SI* value is checked for convergence. If the change in the identified *SI* value is greater than 0.1%, the insulin pharmacokinetic parameters are reassessed and steps 2–4 are repeated. Typically, less than 10 iterations are required and parameter identification can be undertaken in less than a second. *SI* is considered converged once changes between iterations are less than 0.1%.

Insulin sensitivity values from DISTq are calibrated to gain unit equivalence to the EIC and allow a direct comparison in terms of magnitude

$$ISI_{\text{DISTq}} = SI_{\text{DISTq}} \cdot 18\,000 \cdot V_G \cdot G_B \cdot \gamma \cdot \frac{1}{B_W} \tag{11}$$

where $\gamma = 0.5$ is the steady-state ratio between plasma insulin and interstitial insulin [32].

3) OGTT: In this study, the OGTT was used to define the participant's diabetic status. The American Diabetes Association (ADA) criteria for diabetes diagnosis require repeated 2 h glucose measurement of $>$11.0 $\text{mmol} \cdot \text{L}^{-1}$ for a diagnosis of diabetes [33]. The ADA criteria state that a 2 h glucose $>$7.8 $\text{mmol} \cdot \text{L}^{-1}$ can be used to diagnose impaired glucose tolerance (IGT) [33].

The Matsuda index [34] and HOMA_2 scores [35] were calculated from glucose and insulin measurements taken during the OGTT.

E. Statistical Analysis

Equivalence between the DISTq and EIC was assessed via correlation analysis, Bland–Altman plots, and receiver operator curves (ROC). The ROC for the EIC comparison used an arbitrary cutoff value of $ISI_{\text{EIC}} = 1 \times 10^{-2}$ $\text{mg} \cdot \text{L} \cdot \text{kg}^{-1} \cdot \text{pmol}^{-1} \cdot \text{min}^{-1}$, which was approximately the median *ISI* score recorded by the clamp in the cohort. Thus, given the relatively high rate of obesity in the cohort (40%), this median *ISI* may also represent a threshold of elevated metabolic risk [3], [36], [37] providing a further assessment of potential clinical utility. The ROC c-unit was defined as the area under the ROC.

III. Results

DISTq and DISTq30 *ISI* values correlated to the EIC values at $R = 0.76$ and $R = 0.75$, respectively. The Bland–Altman analysis produced a median DISTq and DISTq30 overestimation of the EIC of 13.4% (IQR –24.7–33.1%) and 22.7% (IQR –17.4–41.4%), respectively. The ROC c-units were 0.84 and 0.85, respectively. Fig. 2 shows the correlation, Bland–Altman and

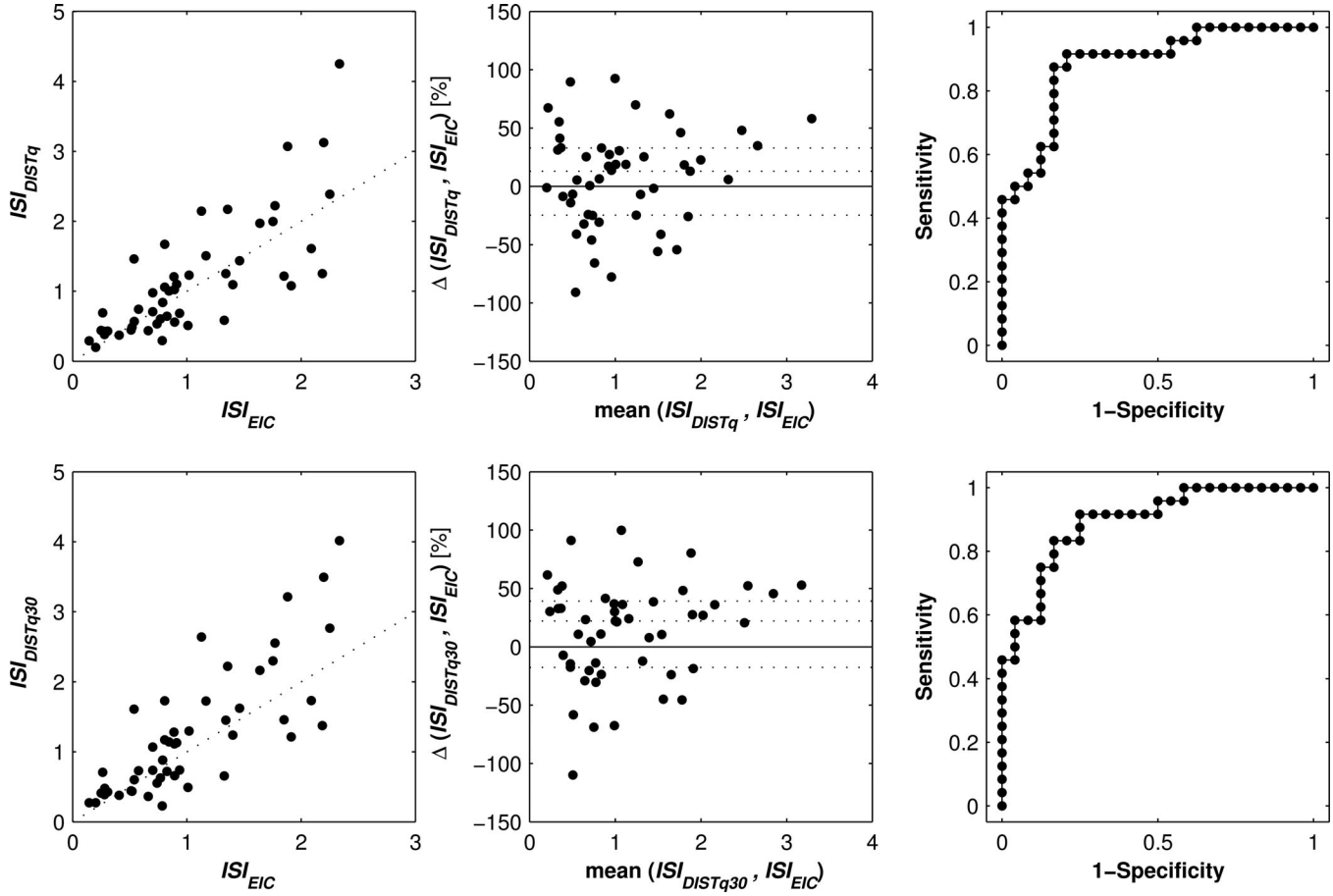

Fig. 2. Correlations (left), proportional Bland–Altman plots (centre) and ROC (right) between the *ISI* values [10^{-2}mg · L · kg^{-1} · pmol^{-1} · min^{-1}] of the DISTq and the EIC (top) and DISTq30 and the EIC (bottom). The correlation plots show the 1:1 line (· · ·) and the Bland–Altman plots show the median and quartiles (· · ·) of the proportional differences in *ISI*.

ROC for DISTq and DISTq30. DISTq and DISTq30 correlated at $R = 0.84$ and $R = 0.86$, respectively, to the fully sampled DISST.

There were no cases of symptomatic hypoglycaemia during the DISST protocol, and participant acceptance was high. According to the ADA criteria for diagnosis of diabetes, one participant met the criteria for diabetes on the basis of the 2 h OGTT glucose measurement, although formal diagnosis would require a second test, and four individuals had impaired glucose tolerance.

It was noted that a single participant had an irregular endogenous insulin production response to the DISST test glucose stimulus, contributing to a disproportionate effect on the correlation and ROC analysis. By self-report, this individual consumed large quantities of sugary "energy" drinks (>1 L/day). The first phase insulin response of this participant (2.8 U) was significantly higher than the upper quartile of the first-phase responses (1.10 U). Omitting data from this participant changed the correlation to $R = 0.78$ for DISTq and $R = 0.80$ for DISTq30, and the ROC c-units became 0.88 and 0.89, respectively.

In this study, $HOMA_2$ values correlated to the EIC at $R = 0.60$ (ROC c-unit $= 0.92$) and the Matsuda index correlated to the EIC at $R = 0.74$ (ROC c-unit $= 0.95$).

IV. Discussion

Formulating the model of glucose and insulin dynamics such that a single model variable is used to define glucose clearance allows DISTq much greater practical model identifiability than the minimal model. Model identifiability was improved to the extent that *SI* values with a high correlation to the gold standard EIC were measured using only 2–4 glucose measurements from a relatively low-intensity 30-min clinical protocol. In contrast, the minimal model requires a 2–3 h intravenous glucose tolerance test (IVGTT) or insulin modified IVGTT test with 10+ glucose and insulin assays to report similar gold standard *SI* correlations [38]–[42]. These results confirm the hypothesis in Docherty *et al*. [13].

Fig. 2 shows that DISTq *SI* and EIC values had a minimal and nonsystemic bias. In data not shown, the correlation between EIC and DISTq is approximately unchanged if the DISTq process is not iterated (i.e., insulin parameters are constant across the cohort and are not a function of *SI*). However, the bias then becomes systemic. Insulin resistant participants have a tendency toward lower insulin clearance rates (see 3, [43]). Hence, if a population value for n_L was used to model an insulin resistant populations test response, their plasma insulin concentrations

would be underestimated. Subsequently, *SI* would be overestimated. The inverse is true for insulin sensitive participants. In confirmation, Yates *et al*. found systemic bias when using a similar methodology without iterative estimation of insulin kinetics [44]. Hence, the improved results and lack of systemic bias are a function of the modeling and identification methods.

The high correlation and limited bias between the DISTq and EIC *SI* values imply that the DISTq would be a suitable EIC surrogate when low-cost or immediate results are desired. In addition, the EIC protocol generates a steady-state, supraphysiological insulin concentration. In contrast, DISTq uses a low-dose insulin bolus to achieve dynamic, physiological insulin excursions. The supraphysiological insulin concentration of the EIC is less efficient due to saturation of insulin action [45], [46]. Hence, the DISTq overestimation of EIC *SI* values may be expected due to saturation effects that are known to affect EIC outcomes [45], [46]. The 30 min 2–4 sample DISTq protocol is considerably less clinically intense than the 3–4 h, 24–30 sample gold-standard EIC test. However, DISTq lacks some of the repeatability of the EIC and the wealth of historical research consolidating the meaning of the EIC metric in the pathogenesis of diabetes and the metabolic syndrome.

By merit of the outcomes of this validation study, DISTq could occupy a low-cost niche in the spectrum of available insulin sensitivity tests. Currently, the homeostasis model assessment (HOMA) is often used in research applications where a low cost and intensity measurement of *SI* is acceptable [47]. The most frequently used form of HOMA requires a single sample, and is thus much less intense than DISTq. However, the true HOMA protocol requires three blood samples taken on three subsequent days [48]. Returning to the clinician for repeated blood tests could be considered more burdensome for the participant than the 30-min DISTq protocol. The DISTq to EIC correlations ($R = 0.75$–0.80) were also in the top end of those reported between the EIC and the HOMA ($R = 0.51$–0.80) [49]–[52]. The correlation between the EIC and the HOMA found in this study was $R = 0.60$. The original HOMA sensitivity metrics were derived via a simple function. However, the more accurate HOMA_2 metric requires lookup charts or a freely available program [53].

The Matsuda index requires a 2-h protocol and four insulin samples to yield a metric that correlates to the clamp at $R = 0.69$–0.74 [34], [54] (including this study). The DISTq protocol is 30 min and does not require insulin samples. However, in contrast to DISTq, the OGTT protocol required to calculate the Matsuda index does not need to be undertaken by someone qualified to administer insulin. Thus, the relative clinical intensity of the tests is ambiguous and dependent on the particular constraints of the situation.

The iterative DISTq parameter identification process outlined in Fig. 1 could be difficult for clinical groups that lack specific computational or numerical expertise. Hence, to overcome this barrier to uptake, the authors have developed a stand-alone computational program that can process input glucose data from the DISST protocol to yield *SI* values. The software will be made freely available upon request to the authors. Overall, DISTq may be considered a suitable alternative to HOMA in applications that require more robust *SI* measurement accuracy or when immediate results may be considered an advantage.

The participant that consumed a lot of sugary drink highlights the limitations of this type of *a posteriori* methodology. In particular, the participant's first phase insulin response seems likely to have adapted to cope with the frequent and sudden influx of glucose [55]. C-peptide measurements taken during the clinical trial (but not used to evaluate DISTq *SI*) showed that the participant's first phase insulin secretion response was 2.8 U. This was well above upper quartile of the cohort first phase responses (1.10 U) and the DISTq estimated secretion rate for this participant (0.46 U). The DISTq equations that predict insulin secretion as a function of *SI* significantly underestimated the insulin response of this participant and *SI* was overestimated. Upon recruitment of this participant, it was suspected that DISTq would greatly overestimate their *SI*. However, due to the recruitment criteria of the study, the test was undertaken and the expected outcome was observed. This result implies that individuals with suspected irregularities in insulin pharmacokinetics (other than IGT) should either undergo a test that incorporates insulin assays, or their DISTq results should be interpreted with scepticism. However, the high correlation between the DISTq and EIC found in this cohort that ranged from very insulin sensitive to very insulin resistant individuals shows that the methodology is relevant and precise for a wide range of physiologies.

V. Conclusion

By formulating a model of glucose and insulin dynamics that defines insulin sensitivity as the only variable to fit glucose decay, practical model identifiability was greatly improved. This improvement in identifiability effectively allowed massive reductions in the cost of the clinical protocol required to gather the requisite data to measure insulin sensitivity. The *a posteriori* method relies on representative insulin pharmacokinetic equations to be used, but was successful for 49 of 50 subjects in this study. DISTq outperforms other low-cost insulin sensitivity tests and illustrates the potential for practical model identifiability methodologies to direct and improve clinical outcomes.

Acknowledgment

The authors would like to thank the nurses at the Christchurch Hospital Endocrine Test Centre for their significant assistance with the clinical trials, and also Dr. J. Willis (Lipid and Diabetes Research Group, Christchurch, New Zealand) for assisting with manuscript preparation.

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Authors' photographs and biographies not available at the time of publication.