Validation and implementation of low-cost dynamic insulin sensitivity tests

Paul D Docherty1, J Geoffrey Chase1, Juliet E Berkeley7, Thomas F Lotz8, Liam M Fisk3, Kirsten A McAuley3, Jim I Mann1

1. Department of Mechanical Engineering University of Canterbury; 2. Christchurch School of Medicine, University of Otago; 3. Edgar National Centre for Diabetes Research, University of Otago, New Zealand

AIM: To provide a low-cost insulin sensitivity test, while maintaining rich information content

The dynamic insulin sensitivity and secretion test (DISST) was designed to capture insulin secretion kinetics and glucose dynamics with a less clinically intense protocol than the euglycaemic clamp (EIC), or IVGTT. DISTq was developed to enable real-time and low-cost identification of insulin sensitivity by using only glucose data. While the DISST directly measures the participant’s insulin response to the test stimulus, DISTq estimates the response with a series of population-derived relationships. The DISST and EIC were undertaken by 50 heterogeneous participants and the insulin sensitivity values of the DISST, DISTq and EIC were compared

Outcomes: Correlation between the gold standard EIC and DISST and DISTq were R=0.81 and R=0.76, respectively

The DISST 50th percentile under-estimation of the EIC was -10.6% (IQR -26.8% to 7%), and ROC c-unit was 0.96. The 90th percentile under-estimation produced by DISTq was 13.4% (IQR -24.7 to 33.1%), and the ROC c-unit was 0.84. Participant tolerance of the DISST protocol was very high. No symptomatic hypoglycaemic incidents were noted.

The DISST was capable of distinguishing clinically important differences in insulin secretion that the EIC could not.

BARRIER TO UPTAKE: The DISST and DISTq parameter identification methods are sometimes considered too complex to apply

Many groups with a primary focus on clinical research can lack access to parameter identification software or mathematical expertise. For the DISST or the DISTq to be used by such groups, some provision must be made for parameter identification.

SOLUTION: A stand-alone, simple-to-use computer program could allow any research group to use the DISST or DISTq.

The Dynamic Insulin Sensitivity and Secretion Test (DISST)

Clinical protocol

The DISST is similar to the insulin-modified intravenous glucose tolerance test (IM-IVGTT) with some important distinctions:

• Uses comparatively low-dose to avoid saturation of insulin-modified uptake of glucose (1, 2)
• Uses a frequently-sampled protocol with a lower overall duration
• Requires one skin puncture
• 5 samples are assayed for C-peptide as well as glucose and insulin

Typical DISST outcomes

The comparatively low clinical intensity of the DISST requires robust modelling and parameter identification approaches to obtain clinically relevant parameter values. In particular:

• C-peptide assays are used to obtain insulin secretion profiles using the deconvolution process of Van Cauter et al. [3]

Insulin pharmacokinetics between the plasma and interstitium are directly modulated with additional resolution provided by insulin secretion profiles.

• Glucose decay is modelled with a single parameter, insulin-sensitivity, to maintain identification stability [6, 7]

• Parameter identification is undertaken by the iterative integral method [6, 7]

Modelling Strategy

The iterative integral parameter identification method (Im-PID) was developed as a simple means to estimate parameters from glucose concentration data. The complete model formulae are summarised in steps 1-5 allows convergence to an accurate insulin sensitivity value. Hence, the iterative process summarised in steps 1-5 allows convergence to an accurate insulin sensitivity value

Hybrid Methods

DISST and DISTq represent two disparate methods of measuring insulin sensitivity from dynamic insulin sensitivity data. While the test stimulus is common between the methods, they have very different assay costs. Hence, a series of methods were proposed to provide a compromise between the distinct strategies of the DISST and the DISTq.

These methods allow optimal test selection for a wide range of clinical applications [9, 10].

Finally the common protocol means that if a lower-resolution test response is too close to a clinical threshold, the sample taken can be re-measured to allow a higher-resolution test, without the need for an additional clinical protocol.

DISST ID program features

1. Can use minute or second resolution
2. Can recognise best parameter identification method for given input data. All of the methods presented in Docherty et al. [9, 10] can be used
3. Allows precise time input
4. Allows differing dosing
5. Provides plots of glucose concentration, insulin concentration and pre-hepatic insulin secretion
6. Outputs all participant specific estimated, a-priori and identified parameter values
7. Identifies assay error and can automatically ignore bad assays during parameter identification, if desired

• Results can be saved to csv
• Batch files can be processed