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An *in-silico* proof-of-concept investigation of a combined glucose-insulin bolus quick dynamic insulin sensitivity test

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ABSTRACT

Background: The 30-min quick dynamic insulin sensitivity test (DISTq30) uses two blood-glucose measurements from a dynamic insulin sensitivity test protocol to provide low-cost, real-time insulin sensitivity (*SI*) measurements. However, the DISTq30 clinical protocol contains a potentially redundant 10-min period between glucose and insulin boluses that occur at $t = 0$ and $t = 10$ min.
Methods: A proposed protocol (DISTq20) reduces the DISTq30 test duration to 20 min and administers a combined 10 g glucose and 1 U insulin bolus at $t = 0$. The proposed protocol was evaluated against the clinically validated DISTq30 in a Monte Carlo analysis. 313 clinical responses to the dynamic insulin sensitivity and secretion tests (DISST) from three different studies were used to provide realistic parameter value sets. These values were used to create realistic *in-silico* responses to DISTq20 and DISTq30 protocols. Each simulated response was 'sampled' at the appropriate times and *SI* was identified 200 times in a Monte Carlo analysis with added random assay error for each protocol and parameter set. In a second analysis, the DISTq20 response was simulated with 0–50% inhibition of the first phase insulin response to assess robustness to this potential effect.
Results: Simulated noise had a very similar effect on DISTq30 and DISTq20 *SI* values ($R = 0.99$). DISTq20 overestimated DISTq30 *SI* by a median 1.7% (IQR −4.3% to 7.3%). The second analysis showed that DISTq20 results were robust to variance in first phase insulin secretion ($R = 0.97$). DISTq20 and DISTq30 both had a median CV of 7.9%.
Conclusions: Inconsequential differences between *SI* values found by the DISTq30 and the DISTq20 *in-silico* indicate that the DISTq20 may produce similar clinical results to the DISTq30. Further analysis showed that the identification method was robust to the assumption of zero insulin suppression.

1. Introduction

Insulin sensitivity (*SI*) tests vary in clinical intensity, assay cost and information yield [1,2]. Dynamic *SI* tests have been proposed as a way of delineating peripheral *SI* from hepatic sensitivity [3,4]. The robust parameter identification of these effects that have very similar structural model roles can be enhanced with incorporation of exogenous insulin in the clinical protocol [5,6]. The insulin modified intravenous glucose tolerance test (IM-IVGTT) and the dynamic insulin sensitivity and secretion test (DISST) incorporate insulin boluses 10–20 min after a glucose bolus. However, when whole body *SI* is desired, delineation of peripheral and hepatic sensitivity is not needed and the delay between the glucose and insulin boluses may represent unnecessary clinical intensity.

This investigation measures the discrepancy between a test that uses a typical separated bolus protocol and one that uses a combined bolus. If the combined bolus protocol yields similar *SI* values to the separated bolus test, a venous puncture can be avoided and the overall clinical intensity of the protocol can be reduced.

The quick DISST (DISTq30) presented by Docherty et al. [7] can yield insulin sensitivity measurements immediately after the 30-min protocol using only glucose measurements. DISTq30 uses the DISST clinical protocol with a 10 g IV glucose bolus at $t = 0$ and a 1 U IV insulin bolus at $t = 10$ min. The DISST requires five glucose, insulin and C-peptide measurements to identify *SI* and endogenous insulin secretion (U_N). In contrast, DISTq30 only uses the $t = 0$ and 30-min glucose assays and the participant's height, weight, sex and age to identify *SI*. This compromise means DISTq30 cannot provide

Abbreviations: DISTq, quick dynamic insulin sensitivity test; DISTq20, 20-minute DISTq; DISTq30, 30-minute DISTq; IM-IVGTT, insulin modified intravenous glucose tolerance test; DISST, dynamic insulin sensitivity and secretion test; OGTT, oral glucose tolerance test; *SI*, insulin sensitivity; U_N, endogenous insulin production; T2DM, type 2 diabetes; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normo-glucose tolerance.

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Table 1
Characteristics of the test participants from the three study cohorts (if multiple tests were undertaken by a single individual, their data from each test is included).

Quartiles	Age	BMI	*SI*[*]	Male/female	T2DM/IGT[†]/NGT
Min	20	19.0	1.26	41/272	4/26/283
Q_1	33	26.3	5.60		
Q_2	42	30.7	7.96		
Q_3	50	35.4	11.71		
Max	69	64.8	50.18		

[*] *SI* identified with fully sampled DISST (units: 10^{-4} L mU^{-1} min^{-1}).
[†] IGT and T2DM identified via the 2 h OGTT glucose assay [15], participants of the pilot investigation did not undertake OGTT and IFG was used instead.

participant-specific endogenous insulin secretion data [7,8] as it estimates the participant's insulin response to the test stimulus via *a-posteriori* relationships between *SI* and key insulin pharmacokinetic rates in an iterative process. The method has shown a positive correlation to the fully sampled DISST ($R = 0.91$) [8–10] and the euglycaemic clamp ($R = 0.76$) [11].

The 10-min period between the glucose and insulin boluses of the fully sampled DISST was designed to allow observation of the participant's endogenous insulin response to the glucose bolus via C-peptide assays. However, as DISTq30 does not measure C-peptide or insulin, this observation cannot be made and the 10-min inter-bolus period may be obsolete. This investigation evaluates this assumption by simulating participant responses to a shortened 20-min protocol (DISTq20) using a single combined glucose and insulin bolus at $t = 0$, and comparing the outcomes to known DISTq30 responses in a Monte Carlo analysis. The goal is to estimate the potential performance of this shorter, much less intense protocol.

2. Methods

2.1. Participants

Three cohorts were used to generate physiologically realistic virtual subjects for this *in-silico* analysis. These cohorts were from the DISST pilot investigation [10,12] ($N = 18$; 46 tests), a dietary intervention study [13] ($N = 73$; 217 tests), and the gold-standard DISST validation study [14] ($N = 50$; 50 tests). In total, 313 DISST raw data sets were available from 141 participants. All studies were conducted in accordance with requirements of New Zealand national ethics committees, and each participant signed informed consent prior to any clinical test. Table 1 summarises characteristics of the test participants.

2.2. Protocols

Participants undertook the DISST in a clinical setting after a 10–12 h overnight fast. The test procedure was undertaken while the participant was seated in a supine position. A cannula was inserted into the antecubital fossa and was used for both bolus administration and drawing of samples. In the pilot investigation [16], samples drawn at $t = -10, 0, 5, 10, 15, 20, 25, 30, 35$, and 45 min were assayed for glucose, insulin and c-peptide. The intervention [13] and validation [14] investigations measured glucose, insulin and c-peptide levels in samples taken at $t = 0$, 5, 10, 20 and 30 min. A 50% dextrose bolus was administered immediately after the $t = 0$ sample and an actrapid insulin bolus was administered immediately after the $t = 10$ min sample. Twenty-eight of the pilot tests and all of the intervention and validation tests used a 10 g glucose bolus, and a 1 U insulin bolus (actrapid). Eleven tests of the pilot investigation used 5 g glucose and 0.5 U insulin boluses, and seven trials used 20 g glucose and 2 U insulin boluses. All samples were assayed for glucose, insulin and C-peptide. Glucose assays were undertaken via the C8000 enzymatic glucose hexokinase assay (Abbott Labs, Abbot Park, IL) for the pilot study; enzymatically with Roche kits and calibrators on a Cobas Mira Analyser (Roche Diagnostics, Mannheim, Germany) for the intervention study; and the YSI 2300 stat plus Glucose and L-Lactate (Yellow Springs Instrument Co., Yellow Springs, OH) in the validation study. Insulin and C-peptide assays were performed using the ELICA immunoassay (Roche Diagnostics, Mannheim, Germany) in the pilot study and Roche Elecsys® after PEG precipitation of immunoglobulins (Roche Diagnostics, Mannheim, Germany) in the validation and intervention studies.

3. Calculation

3.1. Fully sampled DISST parameter identification

The physiological model used in this analysis was developed for use the DISST test [12] and is shown in Eqs. (1)–(3):

$$\dot{G} = p_G(G_B - G) - SI(GQ - G_B Q_B) + \frac{P_X}{V_G} \tag{1}$$

$$\dot{I} = -\eta_T I + \frac{\eta_I}{V_P}(Q - I) + x_L \frac{U_N}{V_P} + \frac{U_X}{V_P} \tag{2}$$

$$\dot{Q} = \frac{\eta_I}{V_Q}(I - Q) - \eta_C Q \tag{3}$$

where G is the glucose concentration (mmol L^{-1}); I and Q are plasma and interstitial insulin concentrations, respectively (mU L^{-1}); P_X and U_X are the exogenous glucose and insulin bolus contents, respectively (mmol min^{-1} and mU min^{-1}); U_N is the endogenous insulin production rate (mU min^{-1}); p_G is the glucose dependent glucose uptake (min^{-1}); n_T and x_L are the fractional and first pass extraction of insulin (min^{-1} and dimensionless, respectively); n_I is the plasma-interstitium insulin diffusion coefficient (L min^{-1}); n_C is the binding rate of insulin to cells (min^{-1}); V_P and V_Q are the plasma and interstitium distributions of insulin (L) and the subscript 'B' denotes the fasting state of the species.

Endogenous insulin production (U_N) profiles for the 313 DISST tests were generated from the C-peptide data using the deconvolution process proposed by Eaton et al. and Van Cauter et al. [17,18]. The methods defined by Lotz et al. [16] were used to identify some a priori insulin pharmacokinetic parameter values. The iterative integral method [8,19] was used to identify the proportional insulin clearance rate (n_T), first pass insulin extraction (x_L), volume of glucose distribution (V_G) and insulin sensitivity (SI) from each test.

These values were used to generate simple mathematical relationships between SI and the key insulin pharmacokinetic rates n_T, U_N and basal insulin (I_B) at a cohort level. These mathematical relationships were used in the DISTq parameter identification process. Linear regression of log–log plots between SI and n_T, I_B and each minute of U_N were used to generate population based exponential functions that were used to predict the un-modelled parameters as functions of SI [11]. The following relationships were defined where SI is in units of 10^{-4} L mU^{-1} min^{-1}:

$$\begin{aligned} I_B &= 49.4(SI)^{-0.89} \\ \eta_T &= 0.070(SI)^{0.34} \\ U_N(0) &= 85.7(SI)^{-0.52} \\ U_N(5) &= 136.7(SI)^{-0.23} \\ U_N(20) &= 186.9(SI)^{-0.74} \end{aligned} \tag{4}$$