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The dynamic insulin sensitivity and secretion test—a novel measure of insulin sensitivity

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ABSTRACT

The objective was to validate the methodology for the dynamic insulin sensitivity and secretion test (DISST) and to demonstrate its potential in clinical and research settings. One hundred twenty-three men and women had routine clinical and biochemical measurements, an oral glucose tolerance test, and a DISST. For the DISST, participants were cannulated for blood sampling and bolus administration. Blood samples were drawn at $t = 0$, 10, 15, 25, and 35 minutes for measurement of glucose, insulin, and C-peptide. A 10-g bolus of intravenous glucose at $t = 5$ minutes and 1 U of intravenous insulin immediately after the $t = 15$ minute sample were given. Fifty participants also had a hyperinsulinemic-euglycemic clamp. Relationships between DISST insulin sensitivity (SI) and the clamp, and both DISST SI and secretion and other metabolic variables were measured. A Bland-Altman plot showed little bias in the comparison of DISST with the clamp, with DISST underestimating the glucose clamp by $0.1{\cdot}10^{-2}{\cdot}mg{\cdot}L{\cdot}kg^{-1}{\cdot}min^{-1}{\cdot}pmol^{-1}$ (90% confidence interval, –0.2 to 0). The correlation between SI as measured by DISST and the clamp was 0.82; the c unit for the receiver operating characteristic curve analysis for the 2 tests was 0.96. Metabolic variables showed significant correlations with DISST SI and the second phase of insulin release. The DISST also appears able to distinguish different insulin secretion patterns in individuals with identical SI values. The DISST is a simple, dynamic test that compares favorably with the clamp in assessing SI and allows simultaneous assessment of insulin secretion. The DISST has the potential to provide even more information about the pathophysiology of diabetes than more complicated tests.

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1. Introduction

Insulin resistance and β-cell dysfunction are prerequisites for the development of impaired fasting glucose, impaired glucose tolerance (IGT), and type 2 diabetes mellitus. However, the lack of a relatively simple test to reliably quantify both insulin sensitivity and secretion makes it difficult to examine heterogeneity in epidemiological studies of prediabetes and diabetes and to explore pathophysiology in studies of prevention and treatment. We have described a simple test, dynamic insulin sensitivity and secretion test (DISST) [1,2], which can provide quantitative measures of insulin sensitivity and insulin secretion.

The present article used a simple version of the DISST that involves 5 blood samples taken over a 35-minute protocol that uses low-dose, intravenous glucose (10 g) and insulin (1 U) boluses as stimuli. Thus, it is relatively short and considerably less labor intensive than the criterion standard glucose clamp. The DISST model and identification method enable the sparse sampling protocol by fitting and refining physiological responses to the measured data [3,4]. Unlike previous models, the DISST model of glucose and insulin kinetics accounts for patient-specific losses of insulin to the liver and the kidneys, saturation of insulin clearance at high concentrations, and diffusion and mass conservation of insulin between the plasma and the interstitium [4]. In addition to assessing insulin sensitivity, the test can be used to assess β-cell function using established methods [5]. This aspect of the DISST is not novel.

The availability of such a test that can physiologically assess insulin sensitivity and simultaneously estimate insulin secretion provides the potential to explore heterogeneity in those who are currently labeled with the diagnosis of metabolic syndrome, prediabetes, or type 2 diabetes mellitus and to further understand responses to treatment with lifestyle measures and pharmacology.

This article provides a validation of the DISST in the assessment of insulin sensitivity and illustrates its potential use.

2. Methods

Data from 2 separate studies undertaken by the same group of investigators have been combined. The first study cohort included 10 lean (body mass index [BMI] <25), 20 overweight (BMI >25 but <30), and 20 obese (BMI >30) participants, with an even sex distribution in each category. The second cohort included 73 women who were considered at risk of metabolic diseases either by virtue of having a BMI greater than 25, or a BMI greater than 23 and a family history of diabetes. Participants were excluded if they had any major medical or psychiatric illness or were known to have diabetes. Ethical approval for the first study was from the Upper South A Regional Ethics Committee. The second study was approved by the University of Otago Ethics Committee.

All 123 participants had weight, waist circumference (the midpoint of the lowest rib and highest part of the hip), and resting blood pressure measured. The 50 participants in the first study underwent a glucose clamp, 4-sample oral glucose tolerance test (OGTT), and DISST protocols within 8 days, with at least 1 day between tests. The tests were given in random order such that each of the 6 possible combinations were equally represented. A prerandomized test order was allocated to each participant based on order of recruitment. Participants of the second study underwent the DISST and the 2-sample OGTT to classify them as having a normal or impaired glucose tolerance or type 2 diabetes mellitus [6]. All participants fasted from 10:00 PM the night before each test, and the tests were begun at 9:00 AM.

2.1. OGTT protocol

Fifty participants from the first study had an OGTT for assessment of insulin sensitivity using the Matsuda method [7]. Participants were given a standard 75-g oral glucose load after a fasting blood sample. Further blood samples were collected at 30, 60, and 120 minutes. Homeostasis model assessment (HOMA) was also calculated for the first study participants using the basal assays of the OGTT and previously published methods [8,9].

2.2. DISST protocol

Participants had a cannula inserted into the antecubital fossa for blood sampling and bolus administration. Blood samples were drawn at t = 0, 10, 15, 25, and 35 minutes; and glucose, insulin, and C-peptide were measured on these samples. A 10-g bolus of intravenous glucose was given at t = 5 minutes, and 1 U of Actrapid insulin was given immediately after the t = 15-minute sample. Participants were required to remain at the clinic for 30 minutes after the test and were provided with a small meal or snack.

The parameter identification methods of dynamic tests (such as the DISST) are sensitive to the timing of samples. Thus, the actual sample times were recorded. The integral method is used to identify model-based insulin sensitivity (SI), glucose distribution volume (Vg), and first-pass (x_L) and subsequent hepatic insulin clearance ($_{nL}$) [3,10]. Metrics of β-cell function are derived from insulin production profiles that are deconvolved from interpolated C-peptide data following the established method of Van Cauter et al [3,5]. The DISST model and identification method are briefly repeated in Appendix A.

Three metrics were used to quantify β-cell function. The basal rate (U_b) indicates the rate of insulin production the participant requires to maintain a constant fasting glucose measurement. The area under the curve (AUC_{10}) measures the first-phase insulin production and is defined as the amount of insulin produced above the basal rate during the 10 minutes after the glucose bolus; AUC_{2nd} quantifies the participant's second phase of insulin production as the total amount of insulin produced during the 20 minutes after the period measured by AUC_{10}.

The DISST method used in this study is a simpler version of the original DISST [3,4], using 5 blood samples instead of 9. The impact of such sparse sampling on insulin sensitivity and insulin secretion metrics has been shown to be limited in previous studies [4,11,12]. Previous analysis by Docherty et al [12] found that insulin sensitivity and production values were

barely affected by the omission of samples from the frequently sampled protocol used in the DISST pilot study. The 5-sample method was not significantly different from the original 9-sample method. The correlations between the outcomes of the pilot sampling protocol and the sampling protocol used here were r = 0.90, 1.0, 1.0, and 0.89 for SI, U_b, AUC_{10}, and AUC_{2nd}, respectively.

2.3. Glucose clamp protocol

The 50 participants in the first study underwent a glucose clamp. Participants had 2 cannulae inserted: one in the antecubital fossa and the other, a retrograde cannula, inserted in the dorsum of the hand. The hand was heated so that arterialized blood was obtained for sampling. Insulin was infused at 280 pmol·min^{-1}·m^{-2} (40 mU·min^{-1}·m^{-2}), and glucose was infused to achieve a target glucose concentration of 4.5 mmol·L^{-1} or at the fasting level if this was between 4 and 5 mmol·L^{-1}. The test lasted for 2 to 2.5 hours, and data from the last 40 minutes were used to calculate insulin sensitivity index (ISI) in mg·L·kg^{-1}·min^{-1}·pmol^{-1} [13]. Participants were required to remain at the clinic for 30 minutes after the test and were provided with a small meal or snack.

2.4. Unit correction

As the standard DISST and the clamp SI values have different units, a conversion needs to be made to compare the magnitude of values across the 2 different tests. The model-based SI identified by the DISST measures the glucose disposal as a function of the available glucose, glucose distribution volume, and the modeled interstitial insulin. The clamp measure is based on the absolute glucose disposal, steady-state plasma insulin concentration, and the participant's body weight. Thus, to achieve common units, the DISST SI values must be converted:

$$ISI_{DISST} = SI_{modeled}\frac{18000 \cdot G_b \cdot Vg \cdot \gamma}{BW},$$

where G_b is the basal glucose concentration (mmol·L^{-1}), Vg is the identified distribution volume of glucose [1], BW is body weight (kg), γ is the steady-state ratio between plasma and interstitial insulin (0.5) [14], and the coefficient of 18 000 is required to convert to the standard units for reporting clamp metrics.

2.5. Laboratory analysis

Glucose values for the first study were analyzed using YSI 2300 STAT Plus glucose and L-lactate analyzer (Yellow Springs Instrument Co., Yellow Spings, Ohio) using whole blood. These were converted to plasma glucose with the equation recommended by the analyzer manufacturer:

$$G_{plasma} = \frac{G_{wholebloodglucose}}{1 - \left(2.4 \cdot 10^{-3} \cdot \text{hematocrit (\%)}\right)}.$$

Plasma glucose levels taken in the second study were measured enzymatically with Roche kits and calibrators on a Cobas Mira analyzer (Roche Diagnostics, Mannheim, Germany). Samples for insulin and C-peptide were separated immediately and frozen. Measurements of insulin were undertaken by the Endolab, Canterbury Health Laboratories, for the first study and by the University of Otago Nutrition Laboratory for the second study. Both laboratories used Roche Elecsys after polyethylene glycol (PEG) precipitation of immunoglobulins. Consistency between laboratories was maintained. All C-peptide measurements were undertaken by Endolab, Canterbury Health Laboratories, using the Roche Elecsys method. Serum cholesterol and triglycerides were measured enzymatically with Roche kits, and high-density lipoprotein (HDL) was measured in the supernatant after precipitation of apolipoprotein B containing lipoproteins with phosphotungstate/magnesium chloride solution [15].

2.6. Statistical methods

The data are presented as means and standard deviations or median and upper and lower quartiles. Correlations were used to describe the associations between the insulin sensitivity values. A Bland-Altman plot was used to compare the DISST with the glucose clamp. Analysis of variance was used to compare the 3 groups derived from the first insulin phase (AUC_{10}) and those derived from the second insulin phase (AUC_{2nd}). Comparisons between those with IGT and those with normal glucose tolerance (NGT) are also presented.

3. Results

The range of DISST insulin sensitivity values for the 123 individuals was 0.2 to 3.4·10^{-4} ·L·pmol^{-1}·min^{-1} with a mean of 1.1 (SD, 0.64) and median of 1.0 (interquartile range [IQR], 0.7-1.4). The range for insulin sensitivity estimated by the glucose clamp (n = 50) was 0.1 to 2.3·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1} with a mean of 1.0 (SD, 0.61) and a median of 0.9 (IQR, 0.6-1.4).

The Bland-Altman plot (Fig. 1) shows the bias between the 2 tests, where the DISST underestimated the glucose clamp

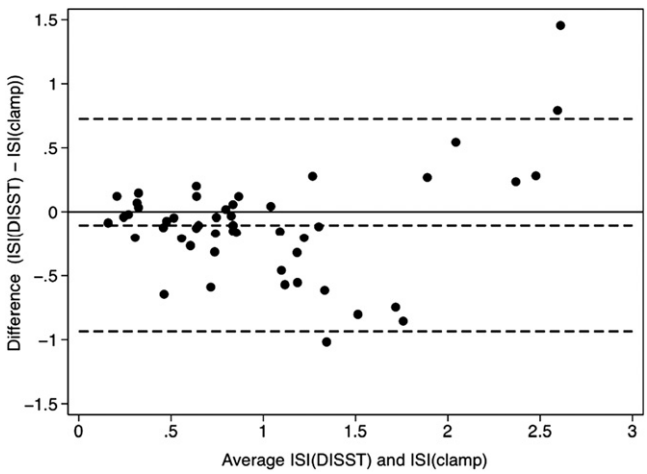

Fig. 1 – The Bland-Altman plot of insulin sensitivity estimates derived from the DISST and the glucose clamp showing the bias between the 2 tests, with the DISST underestimating the glucose clamp insulin sensitivity estimate by 0.1·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1} (95% confidence interval, –0.2 to 0.0). The limits of agreement are –0.9 to 0.7·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1}.

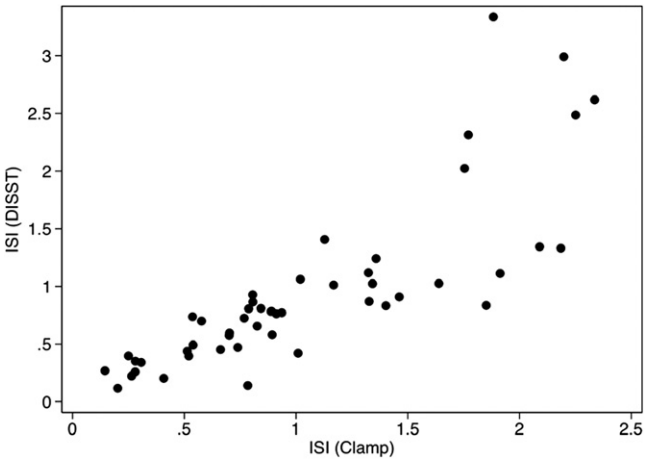

Fig. 2 – The correlation of the DISST and the glucose clamp insulin sensitivity values (units are 10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1}).

Table 1 – Correlation between the DISST insulin sensitivity and variables known to be associated with insulin resistance as well as two simple surrogates for assessing insulin sensitivity: the HOMA and the Matsuda OGTT

	Mean (n = 123)	SD	Correlation with the DISST	P value
Age (y)	42	12.2	−0.16	.09
Waist circumference (cm)	95.5	14.9	−0.51	<.001
BMI (kg/m^2)	31.7	6.90	−0.45	<.001
FPG (mmol/L)	4.8	0.48	−0.34	.002
Fasting triglycerides (mmol/L)	1.30	0.94	−0.27	.002
Fasting HDL cholesterol (mmol/L)	1.19	0.30	0.40	<.001
Fasting insulin (pmol/L)	78.9	75.4	−0.63	<.001
HOMA	2.4	2.27	−0.40	<.001
Matsuda OGTT [a]	16.9	11.0	0.56	<.001

[a] The Matsuda is on 50 participants only.

by 0.1·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1} (95% confidence interval, −0.2 to 0.0). The limits of agreement were −0.9 to 0.7·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1}. Fig. 2 shows the correlation between the DISST and the glucose clamp (r = 0.82). Fig. 3 presents a receiver operating characteristic (ROC) curve for the DISST compared with the glucose clamp (c unit = 0.96 using an insulin resistance cutoff for the glucose clamp of 1.0·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1} [9]).

Correlations between the DISST and the variables known to be associated with insulin resistance are shown in Table 1, as well as the correlations between the DISST and the HOMA and the Matsuda index.

Characteristics of those separated into tertiles of first-phase and second-phase insulin secretion are shown in Tables 2 and 3. Of note, those with IGT were spread evenly across the tertiles of first-phase insulin secretion. However, second-phase insulin secretion was significantly associated with all of the features of the metabolic syndrome. Table 4 compares insulin secretion metrics across the NGT and IGT subgroups. In accordance with previous observations [16-18], the second-phase insulin secretion was significantly higher in those with IGT.

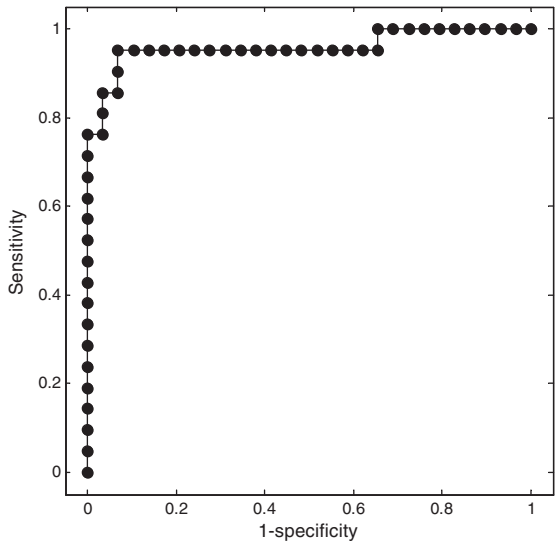

Fig. 3 – The ROC curve of the DISST against the criterion standard, the glucose clamp; c index = 0.96.

Fig. 4 shows the results of the DISST test for insulin sensitivity and insulin secretion metrics for 4 insulin-resistant participants. All of the examples in this figure had the same insulin sensitivity measured by the clamp (0.8·10^{-2}·mg·L·kg^{-1}·min^{-1}·pmol^{-1}); however, the DISST profiles showed clear differences between these individuals. The range of insulin sensitivity estimated by the DISST was 0.95 to 1.36·10^{-4}·L·pmol^{-1}·min^{-1} for these participants. However, of particular note were the distinct insulin production characteristics of these participants. Participants A and B showed contrasting profiles to participants C and D in terms of the magnitude of first-phase release of insulin. Participant C had an increased second phase and blunted first phase of insulin production, which, coupled with an inability to return to the basal glucose concentration within 30 minutes, indicated insulin resistance and β-cell dysfunction for this participant.

No serious adverse events were observed in participants, and there were no episodes of symptomatic hypoglycemia following the DISST.

4. Discussion

The DISST reliably and accurately estimates insulin sensitivity, comparing well with other established and more intensive physiological methods [13,16,19]. In addition, an estimate of β-cell function is obtained including the first and second phases of insulin release. The DISST is well accepted by participants and is straightforward to perform. The low-dose and low-intensity protocol is unique in that it results in insulin

Table 2 – Clinical and biochemical measures by tertiles of the first phase of insulin release (AUC_{10}, from 5 to 15 minutes) during the DISST (n = 123)

	0-4250 pmol of insulin (n = 41)	4251-7000 pmol of insulin (n = 42)	7001-22 000 pmol of insulin (n = 40)	P value
Age (y)	44 (12)	42 (12)	38 (13)	.09
Sex (% female)	82	74	83	.51
Weight (kg)	84.5 (18.3)	86.2 (18.0)	93.4 (24.6)	.12
Waist (cm)	93.0 (15.0)	93.6 (12.7)	100.1 (16.1)	.06
BMI (kg/m^2)	30.4 (6.6)	30.9 (6.0)	33.7 (7.7)	.06
SBP (mm Hg)	120 (14)	120 (14)	123 (19)	.69
DBP (mm Hg)	76 (10)	77 (11)	77 (8)	.89
Fasting triglycerides (mmol/L)	1.30 (1.40)	1.21 (0.57)	1.39 (0.64)	.68
Fasting HDL cholesterol (mmol/L)	1.24 (0.29)	1.22 (0.30)	1.11 (0.29)	.09
FPG (mmol/L)	4.8 (0.5)	4.6 (0.4)	4.6 (0.4)	.01
Fasting insulin (pmol/L)	61.6 (38.7)	66.9 (40.9)	109.1 (114.5)	.007
IGT %	7	12	15	.54
Insulin sensitivity (DISST) [a]	1.2 (0.69)	1.3 (0.69)	0.9 (0.48)	.06

[a] Measured in $10^{-4}{\cdot}L{\cdot}pmol^{-1}{\cdot}min^{-1}$.

concentrations that are comparable with daily excursions and are not affected by dose-dependent saturation effects [20], whereas established tests rely on nonphysiological doses that exceed saturation level for insulin action [21,22]. Thus, the model-based DISST does not require suppression of endogenous insulin production via exogenous insulin infusion as is the case with the simpler glucose uptake to insulin concentration ratio (M/I) model used in the glucose clamp [21,22].

The DISST concurrently allows an assessment of insulin secretion with insulin sensitivity. The insulin secretion identification method was validated by Van Cauter et al [5] and has been used by many leading insulin sensitivity research groups [23-26]. The second-phase values of insulin secretion obtained from the low-intensity DISST correlated well with metabolic risk factors and distinguished IGT and NGT subgroups. The DISST offers the possibility of relating the insulin secretion rate to their insulin sensitivity status, which is potentially useful in research and clinical practice. Insulin secretion typically increases with insulin resistance in the early stages of IGT and type 2 diabetes mellitus, but declines as β-cell function is lost [13,27,28]. Thus, as illustrated in Fig. 4, apparently healthy NGT individuals can have insulin production rates similar to those of individuals that have considerable loss of β-cell function. Current tests do not distinguish between these individuals with different insulin secretion responses [16].

The DISST protocol requires only 5 blood samples. The difference between our reduced-sample approach and previous simplified methods for measuring insulin sensitivity is that we have developed an improved approach to parameter identification methods [10] and have adopted a single-model variable for glucose decay. The identification of 2 metrics that model glucose clearance has been an issue in previous studies using the minimal model approach [29,30]; and strategies used to ameliorate this problem require either Bayesian techniques [31,32] or arduous, clinically intense, frequently sampled protocols. However, it has been shown that fixing the glucose-dependent clearance term (that has limited clinical

Table 3 – Clinical and biochemical measures by tertiles of the second phase of insulin release (AUC_{2nd}, from 15 to 35 minutes) during the DISST (n = 123)

	0-5000 pmol of insulin (n = 44)	5001-8000 pmol of insulin (n = 38)	8001-16 000 pmol of insulin (n = 41)	P value
Age (y)	40 (12.8)	40 (11.4)	45 (12.0)	.12
Sex (% female)	80	79	80	.98
Weight (kg)	76.6 (12.1)	86.0 (14.0)	102.2 (24.8)	<.001
Waist (cm)	84.9 (8.5)	94.8 (11.5)	107.4 (14.3)	<.001
BMI (kg/m^2)	27.2 (4.2)	31.3 (4.7)	36.8 (7.5)	<.001
SBP (mm Hg)	118 (14)	119 (14)	126 (18)	.04
DBP (mm Hg)	74 (9)	76 (8)	79 (12)	.05
Fasting triglycerides (mmol/L)	0.86 (0.29)	1.57 (1.40)	1.51 (1.51)	.005
Fasting HDL cholesterol (mmol/L)	1.29 (0.26)	1.29 (0.32)	0.99 (0.19)	<.001
FPG (mmol/L)	4.4 (0.4)	4.6 (0.4)	4.9 (0.4)	<.001
Insulin (pmol/L)	40.0 (19.2)	67.1 (24.3)	131.5 (108.5)	<.001
IGT %	7	13	15	.48
Insulin sensitivity (DISST) [a]	1.6 (0.69)	1.1 (0.39)	0.7 (0.25)	<.001

[a] Measured in $10^{-4}{\cdot}L{\cdot}pmol^{-1}{\cdot}min^{-1}$.

Table 4 – Measures indicating ß-cell function by glucose tolerance status (n = 123)

	n	Basal insulin production (U_b) [a] (pmol/min) Mean (SD)	First-phase insulin secretion (AUC_{10}) [b] (pmol) Mean (SD)	Second-phase insulin secretion (AUC_{2nd}) [c] (pmol) Mean (SD)
All data	123	235 (103)	6,060 (3,564)	6,889 (3,320)
NGT	109	230 (105)	5,973 (3,578)	6,660 (3,245)
IGT	14	276 (74)	6,739 (3,502)	8,668 (3,487)
P value		.11	.45	.03

[a] U_b is the basal rate of insulin production.
[b] AUC_{10} is the amount of insulin produced 10 minutes after the glucose bolus above the basal rate.
[c] AUC_{2nd} is the total amount of insulin produced between t = 15 and 35 minutes.

value) maximizes identification stability and allows the considerably less intense protocol of the DISST to produce a stable and relevant metric of insulin sensitivity [4,12].

More intensive tests such as the glucose clamp [33] and the intravenous glucose tolerance test (IVGTT) [34] require specialist training for those performing the tests, involve a greater participant burden, and are more costly, all of which generally limit their use to small research studies. They appear to be comparable tests, although the IVGTT, with a coefficient of variation of 14% to 30%, is less reliable than the glucose clamp, with a coefficient of variation of 6% to 10%. The particularly high repeatability has earned the glucose clamp criterion standard status [16]. However, the glucose clamp yields different results at different insulin infusion rates that complicate comparisons between studies [21, 22]. The basic glucose clamp assumes that all endogenous glucose and insulin secretion is fully suppressed, that all glucose uptake is mediated by insulin, and that the uptake rate is proportional to the plasma insulin concentration [33]. In fact, insulin-independent glucose uptake occurs and can be constant (to the brain and the central nervous

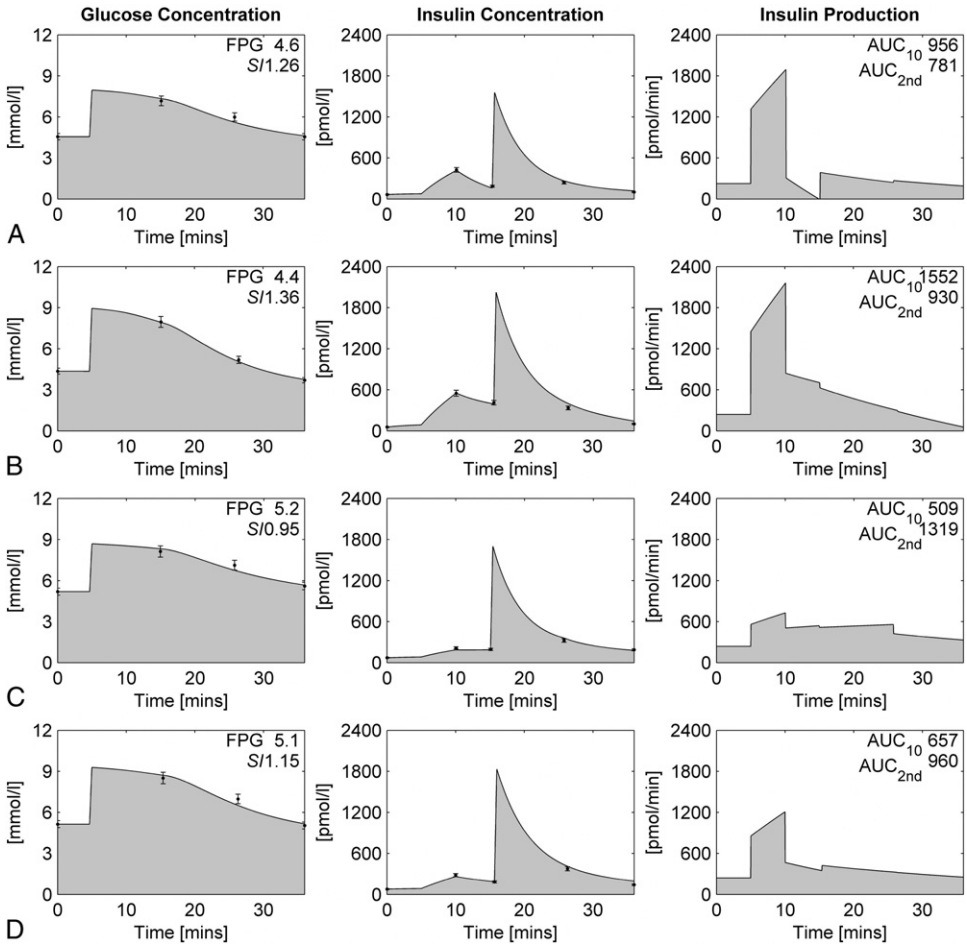

Fig. 4 – Blood glucose, plasma insulin, and insulin production responses of four individuals to the DISST stimulus. The second peak of the insulin concentration is due to the exogenous bolus of insulin used in the DISST protocol.

system) or dependent on glucose concentration [35]. This is accounted for by the DISST; and as a result DISST; SI values are more directly comparable across studies [3].

We report here a strong correlation between insulin sensitivity measured by the DISST and the glucose clamp ($R = 0.82$). It is noteworthy that, on average, the DISST only underestimated the clamp ISI by $0.1{\cdot}10^{-2}{\cdot}mg{\cdot}L{\cdot}kg^{-1}{\cdot}min^{-1}{\cdot}pmol^{-1}$, although there were substantial differences between the 2 protocols. Variables known to be associated with insulin sensitivity correlated well with the DISST (Table 1). There were no notable differences from correlations previously reported with insulin sensitivity measured with the clamp [36]. An earlier study involving repeated tests demonstrated that the DISST was as reliable as the glucose clamp in measuring insulin sensitivity [2]. The ROC analysis, which is usually used to compare 2 very different tests, indicates that the DISST and the glucose clamp are reasonably comparable. Although both tests relate the rate of glucose uptake to an insulin concentration, the clamp involves a steady-state, hyperphysiological protocol with suppression of insulin and glucose production and 2 to 3 hours of frequent sampling, whereas the DISST protocol involves only 35 minute of less frequent sampling and does not significantly suppress endogenous insulin or glucose production. We suggest that DISST insulin sensitivity may be a more representative measure than insulin sensitivity derived from other methods because it is a function of the insulin concentration in the interstitium rather than plasma and accounts for additional non–insulin-dependent glucose uptake. The advantage of minimal sampling, however, may also be considered a potential weakness of the DISST by increasing its susceptibility to measurement error. Furthermore, because the validation study is based on data from a limited number of participants, further independent study is required to fully validate the method.

In conclusion, we believe that the DISST is a relatively low-cost, practical test that yields substantially more information regarding glucose and insulin responses to stimuli than other available tests. The DISST is safe and reliable and allows a reasonable estimation of insulin sensitivity. In addition, estimates of insulin secretion can be obtained at the same time. It is a test that could be applied in clinical or research settings, either where a glucose clamp might be used or in larger trials where either an OGTT or the HOMA would be used. If the DISST were to be applied widely, it has the potential to enhance our understanding of the pathophysiology of those at risk of type 2 diabetes mellitus and to characterize subgroups among this heterogeneous population.

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Conflict of Interest

The authors declare that there is no conflict of interest associated with this manuscript.

Appendix A

The DISST defines the pharmacokinetics/dynamics of C-peptide, insulin, and glucose with a physiological model. The model relates the rate of glucose decay to the concentration of insulin available in the interstitium to provide a metric of insulin sensitivity. The model equations are defined:

Plasma C-peptide

$$\dot{C} = k_2 Y - (k_1 + k_3)C + \frac{uen(t)}{V_p} \tag{1}$$

Interstitial C-peptide

$$\dot{Y} = k_1 C - k_2 Y \tag{2}$$

Plasma insulin

$$\dot{I} = \frac{n_I}{V_p}(Q - I) - n_K I - n_L \frac{I}{1 + \alpha_I I} + \frac{uex(t)}{V_p} + (1 - x_L)\frac{uen(t)}{V_p} \tag{3}$$

Interstitial insulin

$$\dot{Q} = \frac{n_I}{V_q} I - \left(\frac{n_I}{V_q} + n_c\right) Q \tag{4}$$

Glucose

$$\dot{G} = p_{gu}(G_b - G) - SI(GQ - G_b Q_b) + \frac{P(t)}{Vg}, \tag{5}$$

where $k1$ to $k3$ are kinetic parameters (min^{-1}); C and Y are plasma and interstitial C-peptide concentrations, respectively ($pmol{\cdot}L^{-1}$); uen(t) is the time variant rate of insulin production ($pmol{\cdot}min^{-1}$); I and Q are the plasma and interstitial insulin concentrations respectively ($pmol{\cdot}L^{-1}$); V_p and V_q are the distribution volumes of insulin in the plasma and interstitium respectively (L); n_K is the rate of insulin clearance by the kidney (min^{-1}); n_I is the transition rate of insulin between the plasma and interstitium ($L{\cdot}min^{-1}$); n_L is the rate of hepatic insulin clearance (min^{-1}); α_I is the saturation of hepatic insulin clearance ($L{\cdot}pmol^{-1}$); nC is the rate of insulin clearance to cells (min^{-1}); uex(t) is the bolus input of insulin (pmol); x_L is the hepatic first-pass extraction of insulin (L); pgu is the glucose-dependent (insulin-independent) rate of glucose disposal (min^{-1}); SI is the modeled insulin sensitivity ($L{\cdot}pmol^{-1}{\cdot}min^{-1}$); P is the glucose bolus (mmol); Vg is the volume of distribution of glucose (L); G is the glucose concentration ($mmol{\cdot}L^{-1}$); and the $_b$ subscript denotes the basal concentration of the respective species.

The measured C-peptide, insulin, and glucose data are used to identify participant-specific parameters with methods that have been exhaustively defined and justified in previous publications [2-4,10]. However, the methods will be summarized in brief: Initially, a false basal data point with concentrations equal to the measured basal sample was added immediately before the glucose bolus. This ensured that the influence of the basal period on the identified variables was equal across participants. The kinetic parameters of Eqs. [1] and [2] are quantified using functions of participant weight, height, sex, and age that were defined by Van Cauter et al [5]. A piecewise linear interpolation of the C-peptide data was used with these values in a deconvolution of [1] and [2] to produce an endogenous insulin production profile (uen[t]). Finally, SI, Vg, n_L, and x_L were identified using the deconvoluted endogenous insulin production profile, insulin and glucose data, Eqs. [3] to [5], and the integral method [3,10]. Note that the t = 10-minute glucose sample is assumed to be affected by mixing and is thus ignored in the identification of SI and Vg and is omitted from Fig. 4.

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