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

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ARTICLE INFO

Article history:
Received 19 January 2011
Accepted 9 May 2011

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.

Author contributions: KAM contributed to study concept and design, acquisition of data, analysis and interpretation of data, and the writing of the manuscript. JEB contributed to acquisition of data and reviewed manuscript. PDD contributed to acquisition of data, analysis and interpretation of data, and the writing of manuscript. TFL contributed to study concept and design, contributed to pilot work that forms the basis of this paper, and revised the manuscript. LTM contributed to acquisition of data and the writing of the manuscript. GMS contributed to study concept and design, contributed to acquisition of data, and revised the manuscript. SMW was the statistician and contributed to study design, analysis and interpretation of data, and the writing of the manuscript. JGC contributed to study concept and design, analysis and interpretation of data, and the writing of the manuscript. JIM contributed to study concept and design, analysis and interpretation of data, and the writing of the manuscript.

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doi:10.1016/j.metabol.2011.05.009

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