Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 445–447
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Use of oral glucose minimal model–derived index of insulin sensitivity in subjects with early type 1 diabetes mellitus

Kevin M. Krudys[a], Carla J. Greenbaum[b], Catherine Pihoker[c], Paolo Vicini[a,*]

[a]*Department of Bioengineering, Resource Facility for Population Kinetics, University of Washington, PO Box 355061, Seattle, WA 98195, USA*
[b]*Benaroya Research Institute, Diabetes Clinical Research, Seattle, WA 98101, USA*
[c]*Department of Pediatrics, University of Washington, Seattle, WA 98105, USA*

Received 3 August 2006; accepted 29 October 2007

Abstract

Insulin resistance plays an important role during various stages of the type 1 diabetes mellitus disease process. Unfortunately, many of the techniques used to measure insulin sensitivity are experimentally laborious and time-consuming and are thus impractical for larger clinical and population studies. Therefore, in this study, we obtain estimates of insulin sensitivity from a simpler experiment, the oral glucose tolerance test (OGTT), and compare them with those from a frequently sampled intravenous glucose tolerance test (FSIGT) in a population of subjects defined as having early type 1 diabetes mellitus (abnormal 2-hour glucose on OGTT) and a group of healthy controls. A total of 19 subjects were studied. Eight antibody-positive first- or second-degree relatives of patients with type 1 diabetes mellitus and 11 healthy controls underwent both a 3-hour OGTT and an insulin-modified FSIGT on separate days. Indices of insulin sensitivity (S_I) were estimated from the recently derived oral glucose minimal model and the original minimal model of glucose kinetics for the OGTT and FSIGT, respectively. Estimates of S_I from the OGTT correlated closely with those from the FSIGT in both early type 1 diabetes mellitus (r_s=0.76, P = .04) and healthy control (r_s = 0.67, P = .03) populations. This preliminary study demonstrates the usefulness of OGTT-derived estimates of insulin sensitivity in an early type 1 diabetes mellitus population. Given the simplicity of the OGTT relative to the traditional methods of measuring S_I, the oral glucose minimal model may be appropriate for large population studies and clinical trials.

1. Introduction

Although an impairment in insulin secretion due to β-cell destruction is responsible for the pathogenesis of type 1 diabetes mellitus (T1DM), changes in insulin sensitivity may also play a significant role throughout the disease process [1-5]. Therefore, measurement of insulin sensitivity may be important for the design and interpretation of clinical trials involving patients with T1DM.

Because the euglycemic hyperinsulinemic clamp and frequently sampled intravenous glucose tolerance test (FSIGT) methods are impractical for large clinical trials, the oral glucose minimal model [6] represents an attractive alternative to estimate insulin sensitivity from the simpler protocol of the oral glucose tolerance test (OGTT). It has only recently been applied in normal subjects [6], in older people [7], and in the presence of impaired glucose tolerance [8]. We therefore aimed to compare estimates from the oral glucose minimal model against reference estimates obtained from the FSIGT in both healthy subjects and a population of subjects with early T1DM.

2. Subjects, materials, and methods

The database consisted of a total of 19 subjects. Eight subjects were first- or second-degree relatives of patients with T1DM, were islet cell antibody (ICA)-positive, and had a normal fasting but an abnormal 2-hour glucose value (>11.1 mmol/L) after a glucose load. These subjects, originally identified through the Diabetes Prevention Trial–Type 1 Diabetes Mellitus and previously described [9,10], are referred to as the *early T1DM* group. There were 4 men and 4 women, with mean age of 31.1 (range, 13–44) years and body mass index of 24.6 ± 3.9. The other 11 subjects were

* Corresponding author. Tel.: +1 206 616 1133; fax: +1 206 685 3300.
E-mail address: vicini@u.washington.edu (P. Vicini).

0026-0495/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.metabol.2007.10.001

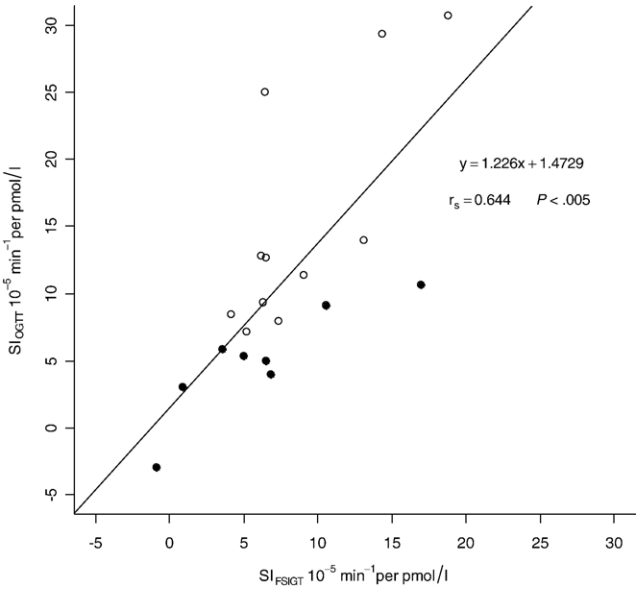

Fig. 1. Comparison between S_I estimated from the OGTT and the FSIGT in healthy controls (white circles) and subjects with early T1DM (black circles).

antibody-negative healthy controls with no relatives with T1DM. There were 6 men and 5 women, with mean age of 26.1 (range, 19-32) years and body mass index of 23.8 ± 2.5.

All subjects signed a written informed consent document before any study procedures. As previously described [9], on separate days, subjects underwent both an insulin-modified (0.02 U/kg for early T1DM subjects and 0.03 U/kg for healthy controls infused over 5 minutes) FSIGT (300 mg/kg) and a 2-hour OGTT (1.75 g/kg, maximum 75 g) sampled every 30 minutes.

Glucose kinetics during the OGTT were described by the previously developed oral glucose minimal model [6], given by:

$$\dot{G}(t) = -[S_G + X(t)] \cdot G(t) + S_G \cdot G_b + \frac{R_a(t)}{V} \quad G(0) = G_b$$
$$\dot{X}(t) = -p_2 \cdot \{X(t) - S_I \cdot [I(t) - I_b]\} \quad X(0) = 0$$

where the overdot represents the first derivative, G is plasma glucose concentration (in millimoles per liter), I is plasma insulin concentration (in picomoles per liter), G_b and I_b are their basal values, X is insulin action (per minute), and V is the volume of distribution of glucose (deciliters per kilogram). Glucose effectiveness, S_G (per minute), reflects the ability of glucose to stimulate glucose disposal and inhibit glucose production. S_I (per minute per picomole per liter) measures insulin sensitivity or the ability of insulin to enhance the glucose stimulation of glucose disposal and glucose inhibition of glucose production. $p2$ (per minute) is the insulin action parameter. R_a, the posthepatic appearance of glucose, was described by a piecewise linear model with breakpoints at the sampling times. Beyond the sampling period, R_a was assumed to obey monoexponential decay with a decay rate of 0.017/min [6]. Furthermore, 86% of the glucose dose is assumed to be absorbed into the circulation [11]. To ensure model identifiability, S_G and V were assumed to be 0.014/min and 1.7 dL/kg, respectively; and maximum a posteriori Bayesian estimation was used by assuming $p2$ is normally distributed with mean 0.03/min and coefficient of variation 20% [6]. The original minimal model of glucose kinetics [12], where S_G, $p2$, S_I, and V were simultaneously estimated, was used to estimate S_I from the FSIGT.

Model parameters were estimated using the software SAAM II (University of Washington, Seattle, WA) [13]. Spearman correlation was used to assess correlation between indices.

3. Results

Insulin sensitivity estimated from the OGTT (S_I^{OGTT}) correlated closely (r_s = 0.64, P = .004) with reference estimates obtained from the FSIGT (S_I^{FSIGT}) (Fig. 1). When each group was analyzed separately, the correlation was stronger in the early T1DM group (r_s = 0.76, P = .04) than in the normal group (r_s = 0.67, P = .03). In absolute terms, S_I^{OGTT} was lower than S_I^{FSIGT} in the early T1DM population (4.98 ± 4.09 vs 6.19 ± 5.64/min/pmol/L), whereas S_I^{OGTT} was higher than S_I^{FSIGT} in the healthy controls (15.32 ± 8.72 vs 8.88 ± 4.58·min/(pmol·l)).

4. Discussion

In this study, we show that estimates of insulin sensitivity derived from the OGTT were closely correlated with analogous estimates from the FSIGT in healthy and early T1DM populations. In keeping with previous observations, S_I^{OGTT} was about twice as high as S_I^{FSIGT} in the healthy population [11,14]. Possible explanations for this phenomenon include the dose of insulin used [15]; the assumptions of S_G and fraction of absorbed glucose; the effect of incretin hormones, specifically GLP−1, during the OGTT; and the influence of the single-compartment assumption of glucose distribution [11]. Although the two estimates are not equivalent, the strong degree of concordance between them suggests that they are measuring the same physiological processes. In the early T1DM group, however, S_I^{OGTT} and S_I^{FSIGT} were roughly of the same magnitude, which may suggest that perhaps some of the aforementioned assumptions of the oral glucose minimal model are more appropriate in individuals at risk for or with T1DM. For example, we have previously demonstrated an impaired incretin response in the individuals with early T1DM [9]. Another possible explanation is that higher levels of doses of insulin, as in our healthy group, have been shown to result in lower estimates of S_I compared with lower doses [15]. Also of note is one subject from the early T1DM group whose S_I^{OGTT} and S_I^{FSIGT} estimates were both negative. This problem has been observed previously for the FSIGT in this population [16]

and is due to a concentration of insulin that is insufficient to exert its influence on the glucose concentration profile. The use of the OGTT may therefore be limited in advanced stages of T1DM where an endogenous insulin response is absent and no exogenous insulin is infused. It is nevertheless reassuring that both S_I^{OGTT} and S_I^{FSIGT} were negative for the same subject.

Because a compensatory hyperbolic relationship exists between insulin secretion and insulin sensitivity [17], accurate measurements of insulin sensitivity may provide a more complete description of the interplay between tissue response to insulin levels and β-cell function during progression to clinical diabetes. This may be important in a population at risk for T1DM or with early T1DM, similar to the one studied here, who often reports conditions of increased insulin resistance such as infection or the onset of puberty before the manifestation of disease. Furthermore, as the frequency of overweight increases in the general population, it is expected that insulin resistance accompanying overweight would become more common in the population at risk for T1DM as well. The estimates of insulin sensitivity described here may be coupled with recently derived indices of β-cell function [18] to provide a global portrait of a patient's metabolic status from an OGTT [19]. Future work is needed to validate these indices in different populations and establish their usefulness in other stages of the disease process.

In conclusion, the present observation that estimates of insulin sensitivity from the OGTT agree with those from the FSIGT in patients with early T1DM suggests that the OGTT may be a practical approach to assess insulin resistance in diabetes prevention and intervention trials.

Acknowledgment

Clinical studies were performed at the University of Washington Clinical Research Center: NCRR Grant M01-RR-00037 with support from an American Diabetes Association Clinical Research Award and Research Associate Career Development Award from the Department of Veterans Affairs (CJG). Samples were assayed using the resources of the University of Washington Diabetes Endocrinology Research Center (Grant 5-P30-DK17047). The work of CJG and CP in this paper is supported by the Juvenile Diabetes Research Foundation Center for Translational Research at the Benaroya Research Institute, Seattle. This work was also partially supported by NIH grant P41 EB-001975, "Resource Facility for Population Kinetics." KMK was supported by NIH grant T32 DE-07023.

References

[1] Leslie RD, Taylor R, Pozzilli P. The role of insulin resistance in the natural history of type 1 diabetes. Diabet Med 1997;4:327-31.
[2] Yki-Jarvinen H, Koivisto VA. Natural course of insulin resistance in type I diabetes. N Engl J Med 1986;315:224-30.
[3] Linn T, Ebener K, Raptis G, Laube H, Federlin K. Natural course of insulin sensitivity and insulin reserve in early insulin-dependent diabetes mellitus. Metabolism 1995;44:617-23.
[4] Hramiak IM, Dupre J, Finegood DT. Determinants of clinical remission in recent-onset IDDM. Diabetes Care 1993;16:125-32.
[5] Greenbaum CJ. Insulin resistance in type 1 diabetes. Diabetes Metab Res Rev 2002;18:192-200.
[6] Dalla Man C, Caumo A, Cobelli C. The oral glucose minimal model: estimation of insulin sensitivity from a meal test. IEEE Trans Biomed Eng 2002;49:419-29.
[7] Basu R, Breda E, Oberg AL, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. Diabetes 2003;52:1738-48.
[8] Dalla Man C, Yarasheski KE, Caumo A, et al. Insulin sensitivity by oral glucose minimal models: validation against clamp. Am J Physiol Endocrinol Metab 2005;289:E954-9.
[9] Greenbaum CJ, Prigeon RL, D'Alessio DA. Impaired beta-cell function, incretin effect, and glucagon suppression in patients with type 1 diabetes who have normal fasting glucose. Diabetes 2002; 51:951-7.
[10] Greenbaum CJ, Cuthbertson D, Krischer JP. Type I diabetes manifested solely by 2-h oral glucose tolerance test criteria. Diabetes 2001;50:470-6.
[11] Caumo A, Bergman RN, Cobelli C. Insulin sensitivity from meal tolerance tests in normal subjects: a minimal model index. J Clin Endocrinol Metab 2000;85:4396-402.
[12] Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol 1979;236:E667-77.
[13] Barrett PH, Bell BM, Cobelli C, et al. SAAM II: simulation, analysis, and modeling software for tracer and pharmacokinetic studies. Metabolism 1998;47:484-92.
[14] Steil GM, Hwu CM, Janowski R, et al. Evaluation of insulin sensitivity and beta-cell function indexes obtained from minimal model analysis of a meal tolerance test. Diabetes 2004;53:1201-7.
[15] Prigeon RL, Roder ME, Porte Jr D, Kahn SE. The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin transport in humans. J Clin Invest 1996;97:501-7.
[16] Finegood DT, Hramiak IM, Dupre J. A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. J Clin Endocrinol Metab 1990;70:1538-49.
[17] Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42: 1663-72.
[18] Toffolo G, Breda E, Cavaghan MK, Ehrmann DA, Polonsky KS, Cobelli C. Quantitative indexes of beta-cell function during graded up and down glucose infusion from C-peptide minimal models. Am J Physiol Endocrinol Metab 2001;280:E2-E10.
[19] Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. Diabetes 2001;50:150-8.