A Model-Based Method for Assessing Insulin Sensitivity From the Oral Glucose Tolerance Test

ANDREA MARI, PHD[1]
GIOVANNI PACINI, DSC (ENG)[1]
ELAINE MURPHY, MD[2,3]
BERNHARD LUDVIK, MD[4]
JOHN J. NOLAN, MD[2,3]

OBJECTIVE — Available insulin sensitivity (IS) methods based on the oral glucose tolerance test (OGTT) are empirical. We used a glucose-insulin model to derive an OGTT-based IS (oral glucose insulin sensitivity [OGIS]) index, which predicts glucose clearance in a glucose clamp. We validated OGIS against clamp data.

RESEARCH DESIGN AND METHODS — OGIS requires glucose and insulin concentrations from a 75-g OGTT at 0, 2, and 3 h (3-h OGTT) or at 0, 1.5, and 2 h (2-h OGTT). The formula includes six constants optimized to match the clamp results. For this purpose, 15 lean nondiabetic subjects (BMI < 25 kg/m^2), 38 obese nondiabetic subjects (BMI > 25 kg/m^2), and 38 subjects with type 2 diabetes randomly underwent an OGTT and a 120 mU $\cdot$ min^{-1} $\cdot$ m^{-2} insulin infusion euglycemic clamp. Glucose clearance (Cl_{CLAMP}), calculated as the ratio of glucose infusion to concentration during the last hour of the clamp, was compared with OGIS. OGIS was also tested on an independent group of 13 subjects with impaired glucose tolerance (IGT).

RESULTS — OGIS and Cl_{CLAMP} were correlated in the whole group ($R = 0.77$, $P < 0.0001$), in the subgroups (lean: $R = 0.59$; obese: $R = 0.73$; type 2 diabetes: $R = 0.49$; $P < 0.02$), and in the independent IGT group ($R = 0.65$, $P < 0.02$). Reproducibility of OGIS and Cl_{CLAMP} were similar (coefficients of variation: OGIS 7.1%, Cl_{CLAMP} 6.4%). OGIS was as effective as Cl_{CLAMP} in discriminating between groups (for OGIS, lean vs. obese: 440 ± 16 vs. 362 ± 11 ml $\cdot$ min^{-1} $\cdot$ m^{-2}, $P < 0.001$; lean vs. type 2 diabetes: 440 ± 16 vs. 239 ± 7, $P < 0.0001$; obese vs. type 2 diabetes: 362 ± 11 vs. 239 ± 7, $P < 0.0001$; results were similar for Cl_{CLAMP}). The relationships between IS and BMI, fasting plasma insulin, and insulin secretion (calculated from the OGTT insulin concentration) were examined. OGIS yielded results similar to Cl_{CLAMP} and fully consistent with established physiological principles. The performance of the index for the 3-h and 2-h OGTT was similar.

CONCLUSIONS — OGIS is an index of IS in good agreement with the clamp. Because of its simplicity (only three blood samples required), this method has potential use for clinical investigation including large-scale epidemiological studies.

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From the [1]Institute of Systems Science and Biomedical Engineering, National Research Council, Padova, Italy; the [2]Department of Endocrinology, St. James's Hospital, Dublin, Ireland; the [3]Department of Clinical Medicine, Trinity College, Dublin, Ireland; and the [4]Division of Endocrinology and Metabolism, Department of Medicine, University of Vienna, Vienna, Austria.

Address correspondence and reprint requests to Andrea Mari, PhD, LADSEB-CNR, Corso Stati Uniti 4, 35127 Padova, Italy. E-mail: mari@ladseb.pd.cnr.it.

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Abbreviations: Cl_{CLAMP}, glucose clearance; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IS, insulin sensitivity; OGTT, oral glucose tolerance test; SSPI, steady-state insulin concentration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Measurement of insulin sensitivity is often of interest in clinical investigation of diabetes and hypertension because of its key role in these diseases. The hyperinsulinemic-euglycemic glucose clamp (1), which is the reference method for insulin sensitivity, has been used successfully in a large number of studies. The clamp technique is experimentally demanding and costly. As research on insulin sensitivity has progressed from case-control studies to larger cross-sectional or longitudinal studies, the clamp has proven to be an impractical tool and therefore rather limited in scope.

Alternative methods applicable to large studies have been proposed. Among these, the intravenous glucose tolerance test with minimal model analysis (2) requires a simpler experimental setup; however, its application to a large number of subjects is problematic because of the necessity of frequent blood sampling and modeling analysis. A method easily applied is the homeostasis model assessment (HOMA) (3), which requires only basal glucose and insulin samples, but its accuracy is not fully demonstrated.

A test widely used for glucose tolerance classification is the oral glucose tolerance test (OGTT). The OGTT, which for its simplicity would be a method suitable for large studies, provides information on insulin secretion and action but does not directly yield a measure of insulin sensitivity. Indeed, various attempts have been made to obtain such a measure (4), and recently, two methods have been proposed and successfully tested against the clamp (4,5). In contrast to these approaches, which are based on empirical formulas, in this study we propose a method based on a physiological glucose-insulin model. Our method provides an index of insulin sensitivity calculated using a model-derived formula from the OGTT glucose and insulin concentration. This index is comparable with the glucose clearance calculated during a clamp and is validated against the clamp method in a population of lean and obese subjects,

Table 1——*Characteristics of the subjects*

	n	Sex (M/F)	Age (years)	Weight (kg)	BMI (kg/m^2)	Basal glucose (mg/dl)	Basal insulin (μU/ml)
Lean subjects	15	15/0	44 ± 3 (30–78)	72 ± 2 (62–88)	23 ± 1 (20–25)	92 ± 2 (77–103)	6 ± 1 (2–15)
Obese subjects	38	35/3	43 ± 1 (28–71)	102 ± 3 (72–136)	33 ± 1 (25–43)	97 ± 2 (82–126)	15 ± 2 (2–73)
Subjects with type 2 diabetes	38	33/5	51 ± 2 (31–72)	102 ± 4 (64–169)	34 ± 1 (21–60)	205 ± 9 (108–343)	22 ± 3 (2–82)
Subjects with IGT	13	10/3	52 ± 2 (39–65)	110 ± 8 (70–173)	34 ± 2 (23–48)	100 ± 11 (81–115)	20 ± 5 (2–60)

Data are means ± SEM (range). Basal glucose and insulin concentration refer to the OGTT sample at time zero.

subjects with impaired glucose tolerance (IGT), and subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects and experimental protocols

A total of 104 subjects were studied: 15 lean nondiabetic (BMI $<$ 25 kg/m^2), 38 obese nondiabetic (BMI $>$ 25 kg/m^2), 38 subjects with type 2 diabetes, and 13 subjects with IGT. Clinical and metabolic characteristics are summarized in Table 1. Subjects were classified according to the World Health Organization criteria (6). Subjects with IGT were included only if they met the criteria on at least two successive OGTTs. Data were compiled and aggregated from a larger database of clamp studies conducted during a 7-year period (1990–1996), several of which have been published previously (7–11). Subjects randomly underwent an OGTT and a glucose clamp study within a 1-month period, at a stable weight and without other interventions. All subjects were in good general health (except for diabetes), and none were taking medications known to affect glucose metabolism. Oral antidiabetic drugs were discontinued for 3 weeks before the study. The purpose, nature, and potential risks of the study were explained before obtaining written consent from the subjects. The study protocols were approved by the Human Subjects Committee of the University of California, San Diego. All subjects were admitted 2–3 days before the respective study to the San Diego Veterans Administration Medical Center's Special Diagnostic and Treatment Unit, and consumed a weight-maintenance diet containing 55% carbohydrate, 30% fat, and 15% protein. Studies were performed at 0800 after a 12-h overnight fast.

Oral glucose tolerance test. A standard 3-h 75-g OGTT was performed. Blood samples were collected at 0, 30, 60, 90, 120, and 180 min for the measurement of plasma glucose and insulin (11).

Glucose clamp. Hyperinsulinemic-euglycemic glucose clamps were performed as described previously (11). A loading dose of insulin was administered in a logarithmically decreasing manner over a 10-min period, followed by a constant infusion rate of 120 mU · min^{-1} · m^{-2} for the next 240 min. In the subjects with IGT, clamp studies were conducted at an insulin infusion rate of 300 mU · min^{-1} · m^{-2}. During the clamp, the serum glucose concentration was maintained at 90 ± 5 mg/dl by monitoring the glucose levels at 5-min intervals and by adjusting the infusion rate of a 20% glucose solution.

Modeling analysis

The present OGTT method for assessing insulin sensitivity is based on an equation that predicts glucose clearance during a hyperinsulinemic-euglycemic clamp using the values of glucose and insulin concentration obtained from an OGTT. The equation is derived from a model of the glucose-insulin relationship, which although simplified, is based on established principles of glucose kinetics and insulin action. The model-derived equation requires the knowledge of parameters that cannot be directly calculated from an OGTT. To circumvent the problem, we have introduced some assumptions and have determined the unknown parameters by matching the OGTT-predicted glucose clearance with the glucose clearance calculated from a clamp. The outline of the modeling analysis is shown in Fig. 1.

Model equations. We assume that the relationship between glucose clearance (Cl, ml · min^{-1} · m^{-2}) and insulin concentration is the linear relationship

$$Cl = Cl_b + S\,\Delta I \qquad (1)$$

where Cl_b (ml · min^{-1} · m^{-2}) is basal glucose clearance, ΔI (μU/ml) is the increment over basal of insulin concentration, and S [(ml · min^{-1} · m^{-2})/(μU/ml)] is the slope of the line. Equation 1 represents the relationship experimentally observed when insulin concentration is in the physiological range (12). Equation 1 is a predictor of glucose clearance at the reference insulin concentration increment ΔI, when Cl_b and S are known.

We describe glucose kinetics during the OGTT with a single-compartment model, which is a reasonable simplification in the OGTT, because changes of glucose fluxes and concentrations are gradual. The model is described by the differential equation

$$V\frac{dG(t)}{dt} = -Cl(t)G(t) + R_a(t) \qquad (2)$$

where G (mg/ml) is glucose concentration, V (ml/m^2) is the glucose distribution volume, Cl (ml · min^{-1} · m^{-2}) is the glu-

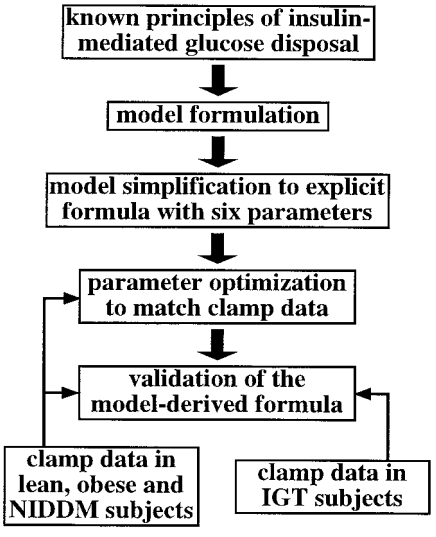

Figure 1——*Outline of the model development and data analysis.*

cose clearance, and R_a ($mg \cdot min^{-1} \cdot m^{-2}$) is the glucose rate of appearance, which is the sum of glucose production and oral glucose appearance. For V, which cannot be determined from the OGTT, we have assumed a value of 10 l/m^2, which represents the total glucose distribution volume (10 $l/m^2 \times 1.7\ m^2/70\ kg = 243\ ml/kg$) (13). The initial steady-state condition for Eq. 2 is $G(0) = R_a(0)/Cl(0)$, where the values at time 0 are the basal values.

We assume that $Cl(t)$ in Eq. 2 is related through Eq. 1 to the insulin concentration increment in a compartment remote from plasma, denoted as $\Delta I_r(t)$ (11,14). With this assumption, Eq. 2 becomes

$$V\frac{dG(t)}{dt} = -[Cl_b + S\,\Delta I_r(t)]G(t) + R_a(t) \quad (3)$$

Equation 3 can be solved for S, treating the other variables as known, and the expression of S thus obtained can be inserted into Eq. 1. Because $Cl_b = P_b/G_b$, where G_b and P_b are basal glucose concentration and production, respectively, the equation for predicting the glucose clearance at the target insulin concentration increment ΔI is the following (see APPENDIX at the end of this article for details):

$$Cl = \frac{\Delta I}{\Delta I_r(t)}\left[\frac{R_a(t) - V dG(t)/dt}{G(t)} + \frac{P_b(\Delta I_r(t)/\Delta I - 1)}{G_b}\right] \quad (4)$$

Equation 4 is the basis for predicting the clamp glucose clearance from the OGTT. However, because several variables in Eq. 4 are unknown, it is necessary to introduce further assumptions. First, we have evaluated the time-dependent terms at $t = 120$ min, i.e., we have used $G(120)$, $dG(120)/dt$, $R_a(120)$, and $\Delta I_r(120)$. This choice is motivated by the fact that glucose disposal, the increase of which follows the increase in plasma insulin, is usually reaching maximum around 120 min (12) and that in the last hour of the OGTT, glucose concentration exhibits a clear downslope from which the derivative of glucose concentration can be safely calculated. Second, we have evaluated $dG(t)/dt$ as $[G(180) - G(120)]/60$. Third, because $R_a(120)$ is expected to depend on the oral glucose dose, we have assumed that $R_a(120)$ is a constant fraction of oral glucose dose D_O (expressed in g/m^2), i.e., $R_a(120) = p_1 D_O$. Fourth, we have calculated $\Delta I_r(120)$ as

$$\Delta I_r(120) = I(120) - I(0) + p_2 \quad (5)$$

where I ($\mu U/ml$) is insulin concentration. Indeed, insulin concentration at the site of action (ΔI_r) is delayed with respect to plasma insulin (11,14). However, because around $t = 120$ min on average the plasma insulin concentration is relatively stable, the difference between the plasma insulin concentration increment and ΔI_r is expected to be small. Furthermore, it was necessary to introduce the parameter p_2 to prevent $\Delta I_r(120)$ from assuming near-zero values when the insulin secretory response is low, which would make the clearance calculated with Eq. 4 very large. Fifth, we have simplified the second fraction in the square brackets of Eq. 4 as

$$\frac{P_b(\Delta I_r(t)/\Delta I - 1)}{G_b} = \frac{p_3}{G(0)} \quad (6)$$

where p_3 is a parameter. This choice is due to the difficulty in formulating an effective expression for P_b and to the limitations of the predictor of ΔI_r. In addition, alternative expressions have been tested that did not improve the performance of the final equation (see CONCLUSIONS). Sixth, we have assumed a fixed value for the target increment in insulin concentration ΔI. We did not fix ΔI a priori but included ΔI among the model parameters to be determined from the data, i.e., $\Delta I = p_4$. Because the glucose clearance predicted by Eq. 4 with the assumptions above is proportional to ΔI, the parameter p_4 can be considered a scaling factor.

With these assumptions and assigning a value to the parameters $p_1 - p_6$, Eq. 4 yields the formula for calculating glucose clearance from the OGTT. However, this glucose clearance value (Cl_{OGTT}) is not directly comparable with that obtained from the euglycemic glucose clamp. In fact, glucose clearance is not independent from glucose concentration, and the glucose levels during the OGTT may be much higher than the clamp levels, particularly in subjects with diabetes. To obtain a prediction of glucose clearance at euglycemia, we have thus introduced a correction for the glycemic level. We assume that the ratio between the clamp glucose clearance at euglycemia (Cl_{EU}) and the glucose clearance calculated from the OGTT (Cl_{OGTT}) is given by

$$\frac{Cl_{EU}}{Cl_{OGTT}} = p_5\left(1 + \frac{p_6}{Cl_{EU}}\right)[G(120) - G_{CLAMP}] + 1 \quad (7)$$

where G_{CLAMP} is the clamp glucose concentration (normally 90 mg/dl), G(120) is considered representative of an average glucose concentration during the OGTT, and p_5 and p_6 are parameters. Equation 7 embodies two principles: *1*) glucose clearance decreases with increasing glucose concentration (the ratio of clamp to OGTT clearance increases linearly as the glucose concentration during the OGTT increases); *2*) the decrease in glucose clearance is more pronounced for low than for high clearance values (the slope of the line is greater for low than for high Cl_{EU}) (15).

Equation 7 is a quadratic equation in Cl_{EU}, which can be solved with standard techniques. Thus, the equation for predicting the clamp glucose clearance from the OGTT includes an equation to calculate Cl_{OGTT}, which is derived from Eq. 4 with the assumptions above and the correction for the glycemic level, which is the solution of Eq. 7 (see APPENDIX at the end of this article for a detailed derivation)

$$Cl_{OGTT} = p_4\frac{p_1 D_0 - V[G(180) - G(120)]/60}{G(120)} + \frac{p_3}{G(0)}}{I(120) - I(0) + p_2}$$

$$B = [p_5(G(120) - G_{CLAMP}) + 1]Cl_{OGTT} \quad (8)$$

$$Cl_{EU} = \frac{1}{2}\left[B + \sqrt{B^2 + 4p_5p_6(G(120) - G_{CLAMP})Cl_{OGTT}}\right]$$

Equation 8 requires the oral dose D_O, the glucose concentration values G(0), G(120), G(180), and the insulin concentration values I(0) and I(120). These data can be specified in different units, provided the parameters $p_1 - p_6$ are scaled accordingly. Table 2 reports G_{CLAMP}, V, and $p_1 - p_6$ for the common and SI units. The values of $p_1 - p_6$ in Table 2 have been determined as described below.

Equation 8 is based on a 3-h OGTT. It is also possible to rederive Eq. 8 for a 2-h OGTT, which is another commonly used OGTT protocol. In this case, in Eq. 8, G(120), G(90), and I(90) replace G(180), G(120), and I(120), respectively. Fur-

Table 2—*Parameters of Eq. 8*

	3-h OGTT ($OGIS_{180}$)		2-h OGTT ($OGIS_{120}$)	
	Common units	SI units	Common units	SI units
p_1	289	2.89	650	6.50
p_2	270	1,618	325	1,951
p_3	$14.0\ 10^3$	779	$81.3\ 10^3$	4,514
p_4	440	2,642	132	792
p_5	$637\ 10^{-6}$	$11.5\ 10^{-3}$	$652\ 10^{-6}$	$11.8\ 10^{-3}$
p_6	117	117	173	173

Parameters differ depending on the units used for measuring glucose concentration, insulin concentration, and the oral glucose dose. The table reports the values for the common units (mg/dl glucose, μU/ml insulin, and g/m^3 oral glucose dose) and for the SI units mmol/l glucose, pmol/l insulin, and $mmol/m^2$ oral glucose dose. The parameters of Eq. 8 not reported in the table are V, 10^4 ml/kg (both common and SI units); and G_{CLAMP}, 90 mg/dl (common units) or 5 mmol/l (SI units). Units for the parameters in the table are not reported, as not relevant.

thermore, in the derivative of glucose concentration, the time interval between glucose measurements is 30 instead of 60 min. Eq. 8 for a 2-h OGTT requires its own parameters, which are also reported in Table 2.

Equation 8 is easily implemented on a spreadsheet (a downloadable version can be found on the World Wide Web at http://www.ladseb.pd.cnr.it/bioing/ogis/home.html). The index of insulin sensitivity yielded by Eq. 8 will be referred here for brevity as oral glucose insulin sensitivity (OGIS), with subscripts "180" and "120" for the 3- and 2-h protocols, where appropriate. The acronym OGIS will also be used more generally to denote the present OGTT method.

Parameter determination. The six parameters p_1– p_6 were determined by fitting the glucose clearance calculated using Eq. 8 (for either the 3-h or the 2-h OGTT) to the clamp glucose clearance in the pooled group of 91 normal subjects, obese subjects, and subjects with type 2 diabetes. The clamp glucose clearance (Cl_{CLAMP}) was calculated as the ratio of the steady-state glucose infusion rate to the steady-state glucose concentration, thus assuming that glucose production is a small fraction of the total glucose turnover (11). Glucose clearance was normalized to the body surface area, calculated from weight and height according to the equation of Gehan and George (16). Least-squares data fitting was performed using Matlab (Mathworks, Natick, MA).

Model test

IGT group. To validate OGIS against the clamp in an independent group of subjects, Eq. 8 was tested on 13 subjects with IGT. Because the clamp insulin dose in these subjects was higher than in the previous group, correlation but not equality between OGIS and Cl_{CLAMP} was expected.

Lower dose insulin clamp. In 12 of the nondiabetic subjects described in Table 1 (age 28–45 years; BMI 21–38 kg/m^2), we compared OGIS with the more usual 40 $mU \cdot min^{-1} \cdot m^{-2}$ insulin infusion glucose clamp.

Reproducibility

Reproducibility of both Cl_{CLAMP} and OGIS was evaluated from duplicate tests in the same subject studied under stable conditions of diet, exercise, and body weight. For the clamp, the group of subjects was composed of 15 nondiabetic males (age 30–61 years; BMI 20–41 kg/m^2) who underwent duplicate clamps within 2.0 ± 0.6 months. For the OGTT, the group was composed of 24 nondiabetic subjects, 9 subjects with type 2 diabetes, and 9 subjects with IGT (36 males, 6 females; age 29–62 years; BMI 22–42 kg/m^2) who underwent duplicate OGTTs within 2.8 ± 0.3 months. Some of these subjects are from the groups described in Table 1.

Reproducibility of the glucose clearance estimate was expressed as an average coefficient of variation, calculated as the ratio between the clearance standard deviation and the mean clearance value in the group. The clearance standard deviation was calculated as the sample standard deviation of the difference between the two clearance estimates, divided by two. This calculation quantifies the standard deviation of the clearance estimation error in the hypothesis that the error has the same variance in all subjects, that it is not correlated between subjects, and that the change in the subject's clearance between the two tests is negligible. The hypothesis that the clearance standard deviation does not depend on the clearance value was tested visually and by regression analysis from the plot of the clearance standard deviation calculated in each subject versus the subject's clearance. The subject's clearance standard deviation was calculated from the two clearance measurements and the clearance from the mean of the two values. To test the concordance between the two clearance measurements, the correlation coefficient between the two values was also calculated.

Comparison with other insulin sensitivity indexes

HOMA. The HOMA index (3) was evaluated as the product of the OGTT glucose and insulin concentration at time 0. Because HOMA provides an index of insulin resistance rather than sensitivity, the expected correlation with the clamp is negative. For comparison with the clamp, we applied a logarithmic transformation of both HOMA and the clamp index, as the relationship between the two indexes was found to be curvilinear.

ISI(composite). The OGTT index of insulin sensitivity [ISI(composite)] (4) was calculated using both the data of the entire 3-h OGTT and the first 2 h of the test. We could not make direct comparison with the clamp (as in ref. 4), because glucose tracer and clamp steady-state insulin concentration (SSPI) were not available in all subjects. We have used the steady-state glucose infusion rate in place of the tracer-calculated glucose utilization rate, and in the 22 subjects who lacked the SSPI measurement, we used the mean SSPI of the 69 subjects in whom insulin concentration was measured.

MCR_{est}(OGTT). The OGTT index of insulin sensitivity [MCR_{est}(OGTT)] (5) was also calculated. Glucose clearance was expressed in $ml \cdot min^{-1} \cdot m^{-2}$ instead of $ml \cdot min^{-1} \cdot kg^{-1}$.

Evaluation of β-cell function

We have analyzed the relationship between insulin sensitivity and β-cell function and compared, in this respect, the clamp and the OGTT method. We have calculated a simple index of β-cell function as the ratio between the area under

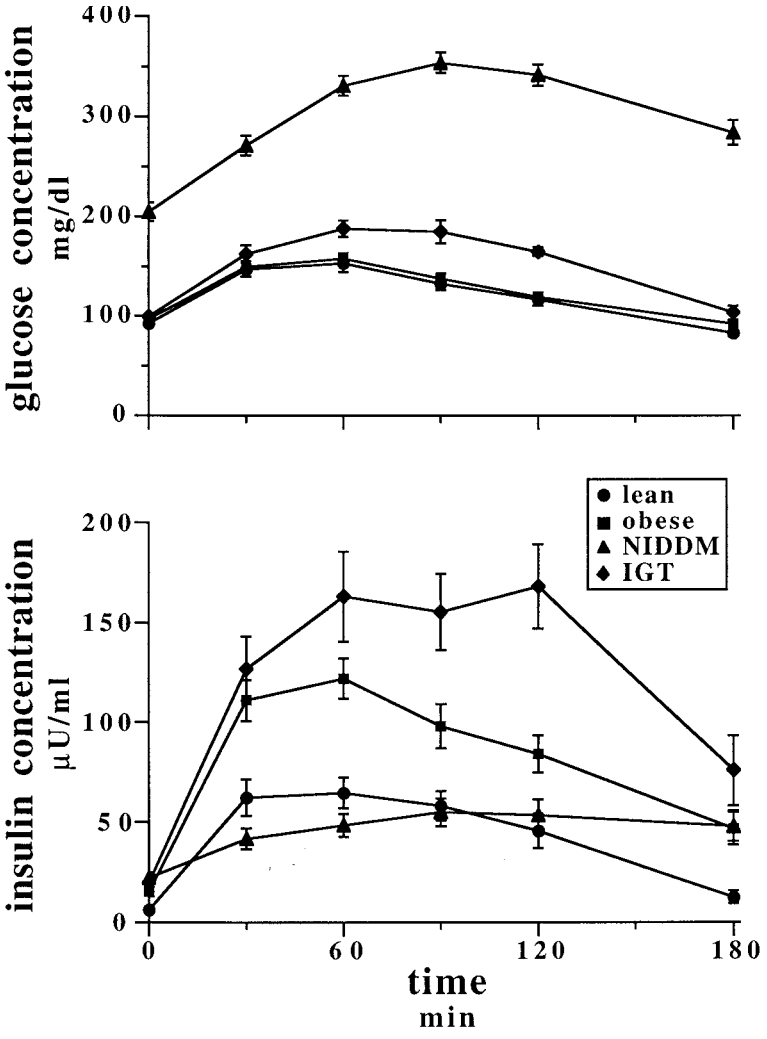

Figure 2—*Mean OGTT glucose and insulin concentrations in lean subjects, obese subjects, subjects with IGT, and subjects with type 2 diabetes.*

the increment in insulin concentration and the area under the increment in glucose concentration during the OGTT (units of the index are μU/mg). The glucose and insulin baseline values used were the minimum values among the six concentration points. Because this index accounts for the glucose levels, it quantifies β-cell sensitivity to glucose, not absolute insulin secretion.

Statistical methods

Data are presented as means ± SEM. The agreement between the model and the clamp glucose clearance was evaluated by standard regression analysis and by using the Bland–Altman method. This provides the confidence interval within which 95% of the differences should lie to state the equivalence ($P < 0.05$) of the two measurements (17). Normality for the whole group of subjects was confirmed by the Shapiro-Wilk W-test (17). The statistical significance of the difference between two groups was assessed with the Mann-Whitney *U* test.

RESULTS

Clamp and OGTT data and model parameters

Figure 2 shows the mean glucose and insulin concentration in the four groups of subjects during the OGTT. The steady-state glucose infusion rates (*M* values, mg · min^{-1} · m^{-2}) during the clamp were as follows: lean subjects 412 ± 15; obese subjects 304 ± 17; subjects with type 2 diabetes 217 ± 13; and subjects with IGT 350 ± 24. The IGT value is not directly comparable with the other three groups, as in IGT a 300 mU · min^{-1} · m^{-2} clamp was performed.

The values of the parameters of Eq. 8 estimated by least-squares are reported in Table 2 for both $OGIS_{180}$ and $OGIS_{120}$.

Comparison with the clamp

$OGIS_{180}$. In the pooled group of lean subjects, obese subjects, and subjects with type 2 diabetes, the mean difference between the glucose clearances determined from clamp and the 3-h OGTT (–5.9 ± 8.0) was not different from zero ($P = 0.47$). The two clearance estimates were equivalent according to the Bland-Altman method. The glucose clearance values are reported in Table 3.

Figure 3 shows the correlation between the glucose clearance calculated from the clamp and from the OGTT. The correlation was statistically significant not only in the pooled group of lean subjects, obese subjects, and subjects with type 2

Table 3—*Glucose clearance (ml · min^{-1} · m^{-2}) calculated from the clamp (Cl_{CLAMP}) and the OGTT ($OGIS_{180}$) and the statistical significance levels of the differences between the groups*

	Cl_{CLAMP}	$OGIS_{180}$
Glucose clearance (ml · min^{-1} · kg^{-1})		
Lean subjects	458 ± 17	440 ± 16
Obese subjects	338 ± 19	362 ± 11
Subjects with type 2 diabetes	242 ± 14	239 ± 7
Subjects with IGT	388 ± 26*	302 ± 17
Significance level of the comparison		
Lean vs. obese subjects	$P < 0.0002$	$P < 0.0007$
Lean subjects vs. subjects with type 2 diabetes	$P < 0.0001$	$P < 0.0001$
Obese subjects vs. subjects with type 2 diabetes	$P < 0.0002$	$P < 0.0001$
Obese subjects vs. subjects with IGT	*	$P < 0.01$

Data are means ± SEM. *Comparison not possible because the clamp dose in subjects with IGT was higher than in the other subjects.

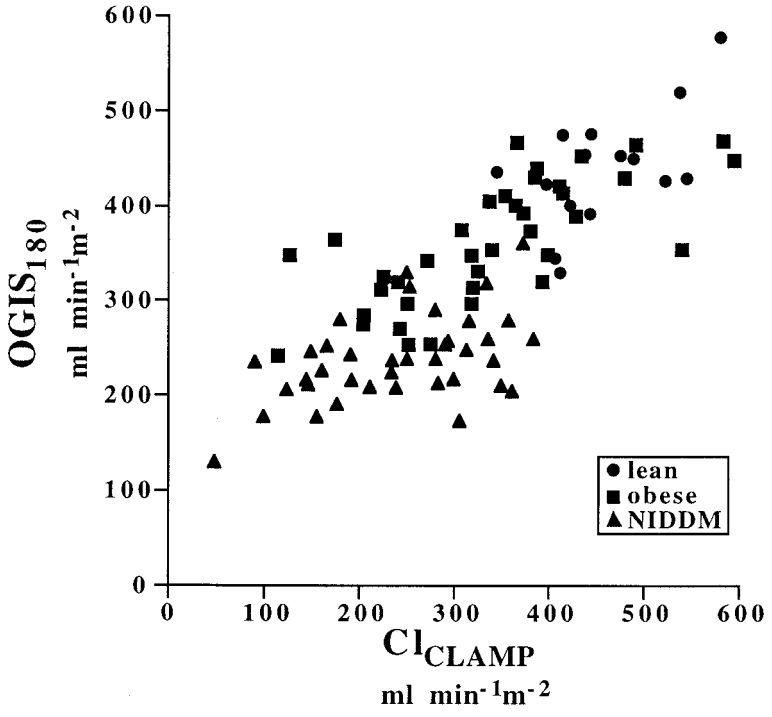

Figure 3—*Comparison between the glucose clearance from the clamp (Cl_{CLAMP}) and the OGTT ($OGIS_{180}$) in lean subjects, obese subjects, and subjects with type 2 diabetes. Correlation results: all subjects,* R = *0.77,* P < *0.0001,* n = *91; lean subjects,* R = *0.59,* P < *0.02,* n = *15; obese subjects,* R = *0.73,* P < *0.0001,* n = *38; subjects with type 2 diabetes,* R = *0.49,* P < *0.002,* n = *38.*

diabetes ($R = 0.77$, $P < 0.0001$, $n = 91$) but also in the individual groups (lean subjects: $R = 0.59$, $P < 0.02$, $n = 15$; obese subjects: $R = 0.73$, $P < 0.0001$, $n = 38$; subjects with type 2 diabetes: $R = 0.49$, $P < 0.002$, $n = 38$). Virtually identical results were obtained for the correlation with the more traditional clamp *M* values, as glucose was kept constant at ~90 mg/dl.

$OGIS_{120}$. The performance of the 2-h OGTT index was only slightly inferior to that of $OGIS_{180}$ (whole group: $R = 0.73$, $P < 0.0001$; lean subjects: $R = 0.53$, $P < 0.05$; obese: $R = 0.57$, $P < 0.0002$; subjects with type 2 diabetes: $R = 0.50$, $P < 0.002$). $OGIS_{180}$ and $OGIS_{120}$ were strongly correlated ($R = 0.92$, $P < 0.0001$).

Model test

In the independent IGT group, the correlation between Cl_{CLAMP} and $OGIS_{180}$ was statistically significant ($R = 0.65$, $P < 0.02$, $n = 13$). In the subset of nondiabetic subjects who underwent insulin infusion glucose clamps at both 40 and the 120 mU · min^{-1} · m^{-2}, $OGIS_{180}$ was correlated with the clamp clearance of 40 mU · min^{-1} · m^{-2} ($R = 0.61$, $P < 0.05$, $n = 12$). $OGIS_{180}$ was also correlated with clamp clearance of 120 mU · min^{-1} · m^{-2} ($R = 0.81$, $P < 0.002$), as expected. The glucose clearance values for the clamps at the two insulin doses were closely correlated ($R = 0.90$, $P < 0.0001$). The correlation between Cl_{CLAMP} and $OGIS_{120}$ was also statistically significant ($R = 0.61$, $P < 0.05$).

Reproducibility

The coefficient of variation of the clearance was 6.4% for Cl_{CLAMP} and 7.1% for $OGIS_{180}$. The two clearance measurements were well correlated both for Cl_{CLAMP} ($R = 0.89$, $P < 0.0001$) and $OGIS_{180}$ ($R = 0.84$, $P < 0.0001$). For both methods, the standard deviation of the clearance in a subject calculated from the two clearance measurements was not correlated with the subject's clearance value (Cl_{CLAMP}: $R = -0.3$, $P = 0.27$; $OGIS_{180}$: $R = -0.06$, $P = 0.70$). Similar results were obtained for $OGIS_{120}$ (coefficient of variation: 7.5%; correlation between two measurements: $R = 0.81$, $P < 0.0001$). For the OGTT, the clearance coefficient of variation was markedly lower than that for the 2-h glucose or insulin concentration (12 and 25%, respectively).

OGIS performance

Differences between groups. The ability to detect significant differences among normal subjects, obese subjects, and subjects with type 2 diabetes was similar for

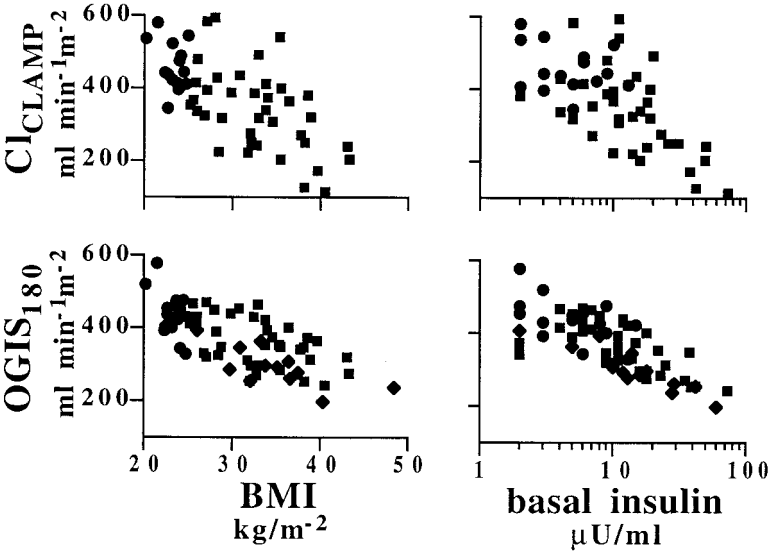

Figure 4—*Relationship between glucose clearance from the clamp (Cl_{CLAMP}) and the OGTT ($OGIS_{180}$) and BMI and basal insulin concentration in lean subjects (●), obese subjects (■), and subjects with IGT (◆). Basal insulin concentration is reported on a log scale to improve reading. Subjects with IGT were not included in the clamp panels because of the different insulin dose. Correlation results are reported in the text.*

the clamp and $OGIS_{180}$ (Table 3). Notably, $OGIS_{180}$ predicted a lower insulin sensitivity in subjects with IGT than in obese subjects (these groups had similar BMIs). This comparison was not possible with the clamp, because obese subjects and subjects with IGT received different insulin doses.

Correlation with BMI and basal insulin. The correlation between glucose clearance (clamp and $OGIS_{180}$) and BMI and basal insulin concentration in normal and obese subjects is shown in Fig. 4. As expected, the correlations were highly significant and equivalent for the two methods ($R = -0.64$ to -0.68, $P < 0.0001$ for all, after bi-logarithmic transformation). Considering normal subjects only, in whom the span of BMI and basal insulin concentration is much reduced, the significance of the correlations for Cl_{CLAMP} was not preserved ($P > 0.25$), whereas it was still present for $OGIS_{180}$ (BMI: $R = 0.57$, $P < 0.05$; basal insulin: $R = 0.55$, $P < 0.05$). In subjects with type 2 diabetes, neither Cl_{CLAMP} nor $OGIS_{180}$ were correlated with BMI ($P > 0.9$ for both). In the independent IGT group, $OGIS_{180}$ was correlated with both BMI and basal insulin (BMI: $R = 0.78$, $P < 0.002$; basal insulin: $R = 0.90$, $P < 0.0001$, after bi-logarithmic transformation), whereas for Cl_{CLAMP}, the correlation was borderline (BMI: $R = 0.55$, $P = 0.052$; basal insulin: $R = 0.45$, $P = 0.13$, after bi-logarithmic transformation).

Correlation with β-cell function. The relationship between $OGIS_{180}$ and Cl_{CLAMP} and the index of β-cell function in normal subjects, obese subjects, and subjects with IGT is shown in Fig. 5. After bi-logarithmic transformation of the variables, the correlation coefficients were as follows: all data pooled, $R = -0.71$, $P < 0.0001$; lean subjects, $R = -0.84$, $P < 0.0001$; obese subjects, $R = -0.66$, $P < 0.0001$; subjects with IGT, $R = -0.81$, $P < 0.001$. As expected, the correlation was not significant in subjects with type 2 diabetes. In the pooled group of normal and obese subjects (IGT could not be included because of the different clamp insulin dose), Cl_{CLAMP} was also inversely correlated with the index of β-cell function ($R = -0.48$, $P < 0.0005$).

Other insulin sensitivity indexes

HOMA. After logarithmic transformation, HOMA was inversely correlated with Cl_{CLAMP}. In the pooled group of 91 subjects, the correlation coefficient was similar to that of $OGIS_{180}$ ($R = -0.75$, $P < 0.0001$). However, in subjects with type 2 diabetes, the correlation was not significant ($R = -0.19$, $P = 0.26$). In contrast to the clamp and OGIS, in subjects with type 2 diabetes, HOMA was correlated with BMI ($R = 0.45$, $P < 0.005$).

ISI(composite). In the entire group of normal subjects, obese subjects, and subjects with type 2 diabetes, ISI(composite), calculated from 2-h OGTT, was correlated with the clamp, but the correlation coefficient was quite low ($R = 0.27$, $P < 0.01$). In part, this mediocre result was due to the presence of two subjects with unusually high values of ISI(composite). These subjects were thus excluded in the subsequent analysis, obtaining a higher correlation coefficient ($R = 0.34$, $P < 0.0001$). Similar results were obtained using 3-h OGTT ($R = 0.39$, $P < 0.0001$) and in the subgroup of subjects in which the steady-state clamp insulin concentration was measured ($R = 0.44$, $P < 0.0002$, 3-h OGTT). Considering the individual groups, however, ISI(composite) was not correlated with the clamp (lean subjects: $R = 0.09$, $P = 0.75$; obese subjects: $R = 0.27$, $P = 0.10$; subjects with type 2 diabetes: $R = 0.06$, $P = 0.72$). In the group of subjects with IGT, the correlation of ISI(composite) with the clamp was better ($R = 0.70$, $P < 0.01$ for 2-h OGTT; results for 3-h OGTT were similar).

MCR_{est}(OGTT). In the entire group of normal subjects, obese subjects, and subjects with type 2 diabetes, MCR_{est}(OGTT) was correlated with the clamp ($R = 0.48$, $P < 0.0001$), excluding one subject with diabetes who had a very low MCR_{est}(OGTT). Considering the individual groups, MCR_{est}(OGTT) was correlated with the clamp only in obese subjects (lean subjects: $R = 0.33$, $P = 0.23$; obese subjects: $R = 0.61$, $P < 0.0001$; subjects with type 2 diabetes: $R = -0.04$, $P = 0.81$, outlier excluded). In the group of subjects with IGT, the correlation of MCR_{est}(OGTT) with the clamp was significant ($R = 0.59$, $P < 0.05$). As

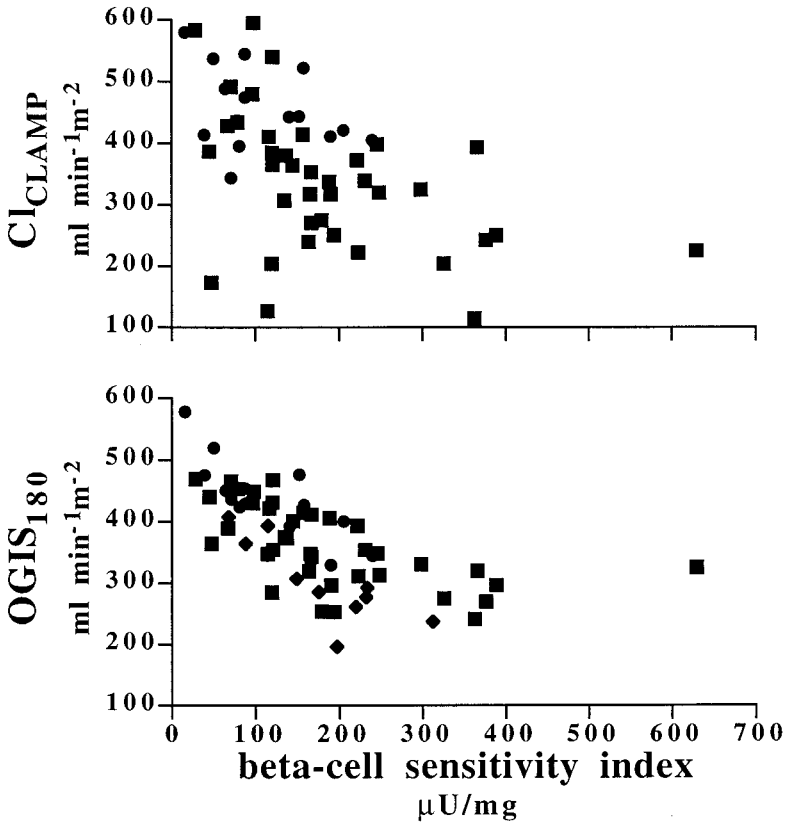

Figure 5—*Relationship between glucose clearance from the clamp (Cl_{CLAMP}) and the OGTT ($OGIS_{180}$) and the index of β-cell sensitivity in lean subjects (●), obese subjects (■), and subjects with IGT (◆). Subjects with IGT were not included in the clamp panel because of the different insulin dose. Correlation results are reported in the text.*

with HOMA, and in contrast to the clamp and OGIS, in subjects with type 2 diabetes, MCR_{est}(OGTT) was correlated with BMI ($R = -0.97$, $P < 0.0001$).

CONCLUSIONS — This study shows that the OGTT method presented here (OGIS) and the glucose clamp give a very similar assessment of insulin sensitivity. The two insulin sensitivity indexes are correlated in four different groups of subjects, spanning a wide spectrum of insulin sensitivity. In particular, the correlation was significant in type 2 diabetes, a condition in which indexes of insulin sensitivity alternative to the clamp often perform unsatisfactorily (for the minimal model, see ref. 18; for HOMA and the other OGTT indexes, see RESULTS). Furthermore, using OGIS, the relationships found between insulin sensitivity and other variables, such as BMI or β-cell function, are in agreement with known facts, and the differences in insulin sensitivity between groups are consistent with current understanding of diabetes pathophysiology. This indicates that OGIS is an adequate index, even if the correlation coefficients with the clamp are not always very high. OGIS has also a good reproducibility, comparable with that of the clamp (coefficients of variation: 7.1 vs. 6.4%, OGIS vs. clamp), despite the fact that the OGTT itself may not be very reproducible (the coefficients of variation of the 2-h glucose and insulin concentration were 12 and 25%, respectively).

A good performance was obtained with both the 2- and 3-h OGTT versions of OGIS. We prefer the 3-h index because the derivative of glucose concentration is better defined in the third hour of the OGTT, and at $t = 120$ min, the rate of glucose appearance, which is quite variable, is smaller and thus has less influence in Eq. 4. However, because $OGIS_{120}$ was only slightly inferior to $OGIS_{180}$, the most widely used 2-h OGTT is sufficient to calculate OGIS reliably, which is an important advantage.

Our modeling approach is based on physiological evidence, with simplifications dictated by the specific characteristics of the OGTT. For glucose kinetics, we have used a single-compartment model, which is a reasonable approximation in the OGTT, because the changes of glucose concentrations and fluxes are gradual. For insulin action, our model is equivalent to the minimal model (2) or to other more sophisticated approaches (14,19). Clearly, our model cannot be completely determined from the OGTT data. The rates of oral and endogenous glucose appearance cannot be calculated without a complex double tracer experiment (20). These processes are quite variable, and an adequate mathematical representation is lacking. The glucose distribution volume is also not determinable. In addition, the experimental information provided by a standard OGTT is limited. Typically, only six glucose and insulin measurements are available, and the data, collected in a clinical environment, may be less precise than those obtained from more rigorously controlled experiments. In this context, the use of heuristic assumptions to obtain a usable equation from the model is unavoidable. The assumptions used to derive Eq. 8 from the more generally valid Eq. 4 were aimed to obtain the best possible agreement with the clamp and have been selected after testing other possible alternatives, which had inferior performance. For instance, we have introduced the simplification of Eq. 6 because more elaborate expressions did not perform better (results not shown). Given the assumptions used to derive Eq. 8, only some of its parameters have a physiological meaning and can be compared with independent references. In particular, there is no expected value for p_4, because it embeds a scaling factor. The parameter p_3 is a composite parameter, because it is related to basal glucose production and to the insulin levels $\Delta I_r(t)$ and ΔI (Eq. 6). Because ΔI is unspecified (see RESEARCH DESIGN AND METHODS), p_3 also lacks a reference value. Similarly, p_2 (Eq. 5) does not have a physiological interpretation. It is introduced to limit the effects of insulin concentration in Eq. 8. The insulin concentration increment has a wide span and is close to zero in some subjects with diabetes. Without p_2, the denominator of Eq. 8, and thus OGIS, would exhibit a variance that would not be compatible with the observed variance in insulin sensitivity. Because p_2 is about 5.5 times the average insulin increment, the influence of insulin concentration on OGIS is much reduced. However, the inclusion of insulin concentration in Eq. 8 is important for obtaining a good correlation with the clamp. The product $p_1 D_O$ represents the glucose rate of appearance at 120 min. The mean value in lean subjects of $p_1 D_O$ is ~ 3 mg · min^{-1} · kg^{-1}, which is in agreement with independent experimental findings (21). The parameters p_5 and p_6 account for a dependence of glucose clearance on glucose concentration (Eq. 7), which was necessary to prevent underestimation of the clamp glucose clearance in subjects with type 2 diabetes, who were markedly hyperglycemic. The predicted reduction of glucose clearance in subjects with type 2 diabetes was ~20% on average; maximum values were ~30%. These results are compatible with published results (15,22). For the 2-h OGTT index ($OGIS_{120}$), the parameters are different because the index is calculated in different conditions. However, the parameters that have some physiological interpretation still have sound values. The value of p_1 is, in fact, higher, because the glucose rate of appearance at 90 min is also higher (21) and the parameters expressing the dependence of glucose clearance on glucose concentration (p_5 and p_6, Eq. 7) are very similar.

We believe that the key of the validity of OGIS is its derivation from a physiological model. The good performance of OGIS can only be due, in part, to the use in Eq. 8 of parameters that have been determined from the same data on which the equation has been subsequently applied. Although this issue requires testing in larger independent groups to be fully resolved, our results do not indicate that this is a major problem for two reasons. First, the number of parameters in Eq. 8 (six parameters) is very small in comparison with the number of subjects (91 subjects). It would not have been possible to obtain a good correlation with the clamp by adjusting these six parameters if the underlying model was not adequate. Second, we have tested the method in an independent group (IGT), in which we have found a correlation with the clamp as good as in the group used to adjust the parameters.

In our data set, the performance of the OGTT-based indexes by Matsuda and DeFronzo (4), Stumvoll et al. (5), and HOMA (3) is inferior to OGIS, but a better comparison would require a totally independent data set. Indeed, in the independent IGT group, the performance of the OGTT methods and HOMA are comparable ($R = 0.6–0.7$). However, at least with our data, the published OGTT methods and HOMA have drawbacks that are overcome by OGIS. In type 2 diabetes, HOMA, ISI(composite), and MCR_{est}(OGTT) do

not correlate with the clamp, whereas OGIS does. This result, which is not in agreement with previous findings (4,23,24), may be due to different characteristics of the subjects with diabetes or the different insulin level in the clamp. Furthermore, the empirical formulas used in HOMA and MCR_{est}(OGTT) introduce spurious results in some cases. In subjects with type 2 diabetes, we have found a strong correlation between HOMA and basal insulin concentration ($R = 0.92$, $P < 0.0001$). Such a correlation was found neither with the clamp ($R = 0.11$, $P = 0.53$) nor with OGIS ($R = 0.16$, $P = 0.35$). This happens because HOMA is the product of glucose and insulin concentration. Similarly, the correlation of HOMA and MCR_{est}(OGTT) with BMI in subjects with type 2 diabetes, which is not found with the clamp and OGIS, is spurious. For HOMA, this originates from the correlation ($R = 0.54$, $P < 0.005$) between BMI and basal insulin, which is used to calculate HOMA. For the method by Stumvoll et al. (5), BMI itself is a variable used to calculate MCR_{est}(OGTT). These results suggest that if the performance of OGIS and the other empirical indexes may be equivalent in some situations, there are also cases in which the use of the model-based index OGIS avoids the drawbacks of empirical formulas.

In the present analysis, OGIS and the clamp give very similar results. However, a caveat is necessary, because OGIS rests on assumptions that the clamp does not require. When it is expected that the mechanisms governing the glucose-insulin relationships are not those postulated here, OGIS may not be accurate. A critical situation could be, for instance, abnormal glucose absorption, which cannot be evaluated from the OGTT without the use of a tracer.

In conclusion, we have shown that the proposed OGTT insulin sensitivity index gives virtually the same results as the clamp when differences between groups are tested and the relationships between insulin sensitivity and other physiological variables are studied. Given its simplicity, this OGTT method is of potential interest in the assessment of insulin sensitivity in large population-based studies. It may also be useful for the assessment of insulin sensitivity in retrospective studies.

APPENDIX — This appendix illustrates, in detail, the derivation of the equation for predicting the clamp glucose clearance from the OGTT (Eq. 8).

During the OGTT, the expression of the glucose clearance given by Eq. 1 becomes

$$Cl(t) = Cl_b + S\,\Delta I_r(t) \tag{9}$$

where $\Delta I_r(t)$ is the insulin concentration increment in the remote compartment. By inserting Eq. 9 into Eq. 2, we obtain

$$V\frac{dG(t)}{dt} = -[Cl_b + S\,\Delta I_r(t)]G(t) + R_a(t) \tag{10}$$

Eq. 10, solved for S, yields

$$S = \frac{\dfrac{R_a(t) - V dG(t)/dt}{G(t)} - Cl_b}{\Delta I_r(t)} \tag{11}$$

which can be substituted into Eq. 1 to calculate glucose clearance at the insulin concentration increment ΔI:

$$\begin{aligned} Cl = Cl_b + S\,\Delta I &= Cl_b \\ &+ \frac{\dfrac{R_a(t) - V dG(t)/dt}{G(t)} - Cl_b}{\Delta I_r(t)}\Delta I \\ &= \frac{\Delta I}{\Delta I_r(t)}\left[\frac{R_a(t) - V dG(t)/dt}{G(t)}\right. \\ &\left. + Cl_b(\Delta I_r(t)/\Delta I - 1)\right] \end{aligned} \tag{12}$$

Basal glucose clearance is related to basal glucose production (P_b) and concentration (G_b) by the equation

$$Cl_b = \frac{P_b}{G_b} \tag{13}$$

which can be substituted into Eq. 12 to obtain Eq. 4.

The assumptions specified in the methods section are:

$$G(t) = G(120) \tag{15a}$$

$$dG(t)/dt = [G(180) - G(120)]/60 \tag{15b}$$

$$R_a(t) = R_a(120) = p_1 D_0 \tag{15c}$$

$$\Delta I_r(t) = \Delta I_r(120) = I(120) - I(0) + p_2 \tag{15d}$$

$$\frac{P_b(\Delta I_r(t)/\Delta I - 1)}{G_b} = \frac{p_3}{G(0)} \tag{15e}$$

$$\Delta I = p_4 \tag{15f}$$

These assumptions transform Eq. 4 into:

$$Cl = p_4\frac{\dfrac{p_1 D_0 - V[G(180) - G(120)/60]}{G(120)} + \dfrac{p_3}{G(0)}}{I(120) - I(0) + p_2} \tag{16}$$

which is the expression of Cl_{OGTT} as given by Eq. 8.

The expression of Cl_{EU} in Eq. 8 is the solution of Eq. 7, which can be rearranged in the standard form of a quadratic equation in the unknown Cl_{EU} as

$$\begin{aligned} Cl_{EU}^2 - [p_5(G[120] - G_{CLAMP}) + 1] \\ Cl_{OGTT}Cl_{EU} - p_5 p_6[G(120) - G_{CLAMP}] \\ Cl_{OGTT} = 0 \end{aligned} \tag{17}$$

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