Insulin Sensitivity Indices Obtained From Oral Glucose Tolerance Testing

Comparison with the euglycemic insulin clamp

MASAFUMI MATSUDA, MD, PHD
RALPH A. DEFRONZO, MD

OBJECTIVE — Several methods have been proposed to evaluate insulin sensitivity from the data obtained from the oral glucose tolerance test (OGTT). However, the validity of these indices has not been rigorously evaluated by comparing them with the direct measurement of insulin sensitivity obtained with the euglycemic insulin clamp technique. In this study, we compare various insulin sensitivity indices derived from the OGTT with whole-body insulin sensitivity measured by the euglycemic insulin clamp technique.

RESEARCH DESIGN AND METHODS — In this study, 153 subjects (66 men and 87 women, aged 18–71 years, BMI 20–65 kg/m^2) with varying degrees of glucose tolerance (62 subjects with normal glucose tolerance, 31 subjects with impaired glucose tolerance, and 60 subjects with type 2 diabetes) were studied. After a 10-h overnight fast, all subjects underwent, in random order, a 75-g OGTT and a euglycemic insulin clamp, which was performed with the infusion of [3-^{3}H]glucose. The indices of insulin sensitivity derived from OGTT data and the euglycemic insulin clamp were compared by correlation analysis.

RESULTS — The mean plasma glucose concentration divided by the mean plasma insulin concentration during the OGTT displayed no correlation with the rate of whole-body glucose disposal during the euglycemic insulin clamp ($r = -0.02$, NS). From the OGTT, we developed an index of whole-body insulin sensitivity (10,000/square root of [fasting glucose × fasting insulin] × [mean glucose × mean insulin during OGTT]), which is highly correlated ($r = 0.73$, $P < 0.0001$) with the rate of whole-body glucose disposal during the euglycemic insulin clamp.

CONCLUSIONS — Previous methods used to derive an index of insulin sensitivity from the OGTT have relied on the ratio of plasma glucose to insulin concentration during the OGTT. Our results demonstrate the limitations of such an approach. We have derived a novel estimate of insulin sensitivity that is simple to calculate and provides a reasonable approximation of whole-body insulin sensitivity from the OGTT.

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The maintenance of normal glucose homeostasis involves the simultaneous and coordinated roles of the pancreatic β-cells, the liver, and the peripheral tissues, primarily muscle (1). Whole-body insulin sensitivity can be measured with the euglycemic insulin clamp technique (2). By combining the euglycemic clamp with a glucose tracer, one can quantitate the separate contributions of peripheral tissues (muscle) and the liver to whole-body insulin sensitivity (3). However, the oral glucose tolerance test (OGTT) is the most commonly used method to evaluate whole-body glucose tolerance in vivo. Although many attempts have been made to assess insulin sensitivity from the OGTT (4,5), it has been difficult to derive meaningful information about whole-body, peripheral tissue, or hepatic sensitivity to insulin from the results of the OGTT.

The product of the glucose area under the plasma glucose curve and insulin area under the plasma insulin curve has been used as an index of insulin resistance (6,7). Although it is intuitively obvious that the existence of an elevated plasma insulin concentration in the presence of a high plasma glucose concentration indicates a state of insulin resistance, this concept has not been validated. Berson and Yalow (8,9), in their initial publication of the insulin assay, were the first to suggest the use of the product of the area under the curves (AUCs) for glucose and insulin as an index of whole-body insulin sensitivity. More recently, Belfiore et al. (10) proposed a hyperbolic function conversion of the product of the glucose and insulin (AUC) to derive an index of insulin sensitivity. Other investigators have used an estimate of glucose uptake during the OGTT divided by the log of the plasma insulin concentration to provide an index of insulin sensitivity (11,12), and this index has been used in some epidemiological studies (13,14). However, in none of these publications was the proposed index of insulin sensitivity validated by comparing it with the direct measurement of insulin-mediated glucose disposal.

Several authors have proposed the use of the glucose/insulin (G/I) ratio (absolute or incremental responses) as an index of insulin sensitivity (5,15,16). Again, no previous study has related the G/I ratio during the OGTT with the direct measurement of insulin sensitivity using the euglycemic insulin clamp. Turner and colleagues (17–19) proposed the homeostatic model assessment (HOMA) to provide an index of insulin sensitivity. This approach, which relies on the product of fasting plasma glucose (FPG) and fasting plasma insulin (FPI) concentrations, has been evaluated in several

From the Diabetes Division, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Address correspondence and reprint requests to Ralph A. DeFronzo, MD, Diabetes Division, Department of Medicine, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284-7886. E-mail: defronzo@uthscsa.edu.

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Abbreviations: AUC, area under the curve; EGP, endogenous glucose production; FPG, fasting plasma glucose; FPI, fasting plasma insulin; G/I, glucose/insulin; HGP, hepatic glucose production; HOMA, homeostatic model assessment; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; R_d, rate of whole-body glucose disposal; SSPI, steady-state plasma insulin.

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

Table 1—*Subject characteristics*

	Normal	IGT	Diabetic	Total
n (M/F)	62 (25/37)	31 (8/23)	60 (33/27)	153 (66/87)
Age (years)	37 ± 2	40 ± 2	50 ± 1	43 ± 1
BMI (kg/m^2)	29 ± 1	31 ± 1	33 ± 1	31 ± 1
FPG (mg/dl)	93 ± 1	96 ± 1*	149 ± 5*	116 ± 3
FPI (μU/ml)	11 ± 1	14 ± 1*	18 ± 1*	14 ± 1

Data are means ± SEM. *$P < 0.001$ vs. subjects with normal glucose tolerance.

recent publications (20,21) and has been shown to provide a reasonable estimate of tissue sensitivity to insulin. Based on the aforementioned problems in assessing insulin sensitivity from the plasma glucose and plasma insulin concentrations in the fasting state and during the OGTT, it is surprising that so few studies have attempted to validate these indices by comparing them with insulin sensitivity measured directly with the euglycemic insulin clamp technique.

In this study, we propose a simple index of whole-body insulin sensitivity derived from the OGTT. This index represents a composite of both hepatic and peripheral tissue sensitivity to insulin. We also evaluated previous indices derived from FPG and FPI concentrations during the OGTT by comparing them with the rate of insulin-mediated glucose disposal during the euglycemic insulin clamp.

RESEARCH DESIGN AND METHODS

Subjects

In this study, 153 subjects with varying degrees of glucose tolerance underwent a euglycemic insulin clamp study (2) and a 75-g OGTT. Subjects were divided into three groups (normal glucose tolerance, *n* = 62; impaired glucose tolerance [IGT], *n* = 31; and type 2 diabetes, *n* = 60) based on the new criteria of American Diabetes Association (22). As a whole, the subjects had a wide range of obesity, with BMI varying from 19.9 to 64.5 kg/m^2. Of the subjects with normal glucose tolerance, 24 had a BMI <27 kg/m^2; 6 of the subjects with IGT had a BMI <27 kg/m^2, and 11 of the diabetic subjects had a BMI <27 kg/m^2. The characteristics of the study population are shown in Table 1. None of the diabetic patients were treated with insulin, metformin, or troglitazone. For subjects who were taking sulfonylureas, the medication was stopped 2 days before the study. Subjects were not taking any other drugs known to affect glucose tolerance. All studies were carried out at the Clinical Research Center of the University of Texas Health Science Center at San Antonio. The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and informed written consent was obtained from each subject before participation.

Euglycemic insulin clamp

After a 10- to 12-h overnight fast, subjects were admitted to the Clinical Research Center at 7:00 A.M. A polyethylene cannula was inserted into an antecubital vein for the infusion of all test substances. A second catheter was inserted retrogradely into an ipsilateral wrist vein on the dorsum of the hand for blood sampling, and the hand was kept in a heated box at 65°C. A prime (20 μCi) continuous (0.2 μCi/min) infusion of [3-^{3}H]glucose (DuPont-NEN, Boston, MA) was given for 120 min. In diabetic subjects, the prime was increased in proportion to the elevation in FPG concentration as follows: 20 μCi × FPG/90 mg/dl. During the last 30 min of the basal equilibration period (120 min in control and IGT subjects, 180 min in type 2 diabetic subjects), plasma samples were taken at 5- to 10-min intervals for determination of plasma glucose and insulin concentrations and tritiated glucose radioactivity. After the basal equilibration period, insulin was administered as a prime continuous infusion at the rate of 40 mU · m^{-2} · min^{-1} for 120 min as previously described (2). The plasma glucose concentration was measured every 5 min after the start of the insulin infusion, and a variable infusion of 20% glucose was adjusted based on the negative feedback principle to maintain the plasma glucose level at 90 mg/dl with a coefficient of variation <5%. Plasma samples were collected every 15 min from 0 to 90 min and every 5–10 min from 90 to 120 min for determination of plasma glucose and insulin concentrations and tritiated glucose radioactivity.

OGTT

At 8:00 A.M., after a 10- to 12-h overnight fast, subjects received a 75-g OGTT. Blood samples were taken at −30, −15, 0, 30, 60, 90, and 120 min for the measurement of plasma glucose and insulin concentrations.

Analytical determinations

Glucose was analyzed with a Beckman II glucose oxidase analyzer (Fullerton, CA). Plasma insulin (Coat A-Coat; Diagnostic Products, Los Angeles, CA) concentration was measured by radioimmunoassay. Plasma [3-^{3}H]glucose radioactivity was determined with a Beckman LS5000 LE liquid scintillation counter (Fullerton, CA) after deproteinization (Somogyi procedure) of plasma samples and evaporation of ^3H_2O. Glucose metabolism during the basal state and during the euglycemic insulin clamp was determined with Steele's non–steady-state equation (23) and a distribution volume of 0.65. Endogenous glucose production (EGP) rate was calculated by subtracting the exogenous glucose infusion rate from the rate of total glucose appearance.

Calculations

The direct measurement of hepatic insulin sensitivity is based on the following logic. In the postabsorptive state, the higher the EGP and the higher the FPI concentration, the greater the severity of hepatic insulin resistance. Because >75% of EGP originates in the liver (24), we use EGP and hepatic glucose production (HGP) interchangeably in the following discussion. Conversely, the inverse of the product of EGP and FPI provides a direct measure of hepatic insulin sensitivity, and the following can be developed:

$$\text{Hepatic insulin sensitivity} = \frac{1,000}{\text{EGP} \times \text{FPI}} \quad (1)$$

where 1,000 simply represents a constant that allows one to obtain numbers ranging from 0 to 10.

In the postabsorptive state, most glucose uptake occurs in insulin-independent tissues (25–28). Consequently, the FPG concentration is largely determined by the rate of basal EGP. Therefore, Eq. 2 can be rewritten as follows:

$$\text{Hepatic insulin sensitivity} = \frac{k}{\text{FPG} \times \text{FPI}} \quad (2)$$

It should be noted that Eq. 2 is mathematically equivalent to the reduced formula of the HOMA model (17) where $k = 22.5 \times 18$. We will refer to this insulin sensitivity index (ISI) as ISI(HOMA).

During the euglycemic insulin clamp, whole-body glucose disposal (R_d) was measured directly from the tritiated glucose turnover data. The direct measure of whole-body insulin sensitivity during the insulin clamp is calculated as follows:

$$R_d \div \text{SSPI} \quad (3)$$

where SSPI is the steady-state plasma insulin concentration during the last 60 min of the insulin clamp.

During the oral glucose load, the suppression of HGP is much less complete than during the euglycemic insulin clamp (29). Thus, insulin sensitivity during the oral glucose load approximately equally reflects both suppression of HGP and glucose disposal by all tissues in the body (30). It follows that the more resistant the liver and peripheral tissues are, the greater the rise will be in mean plasma glucose concentration during the OGTT. Therefore, whole-body insulin sensitivity during the OGTT is inversely proportional to the product of the mean plasma insulin and mean plasma glucose concentrations. A composite measure of whole-body insulin sensitivity that encompasses both hepatic and peripheral tissues can be derived by combining the preceding ISI during the OGTT with that obtained during the basal state (Eq. 1); the latter primarily reflects hepatic insulin sensitivity. This composite whole-body ISI during the OGTT [ISI(composite)] is shown by the following:

$$\frac{10{,}000}{\sqrt{(\text{FPG} \times \text{FPI}) \times (\text{Mean OGTT glucose concentration} \times \text{mean OGTT insulin concentration})}} \quad (4)$$

where 10,000 simply represents a constant that allows one to obtain numbers ranging from 0 to 12. Square-root conversion was used to correct the nonlinear distribution of values.

The above index of whole-body insulin sensitivity during the OGTT was compared with the measurement of insulin-mediated glucose disposal divided by the SSPI concentration during the euglycemic insulin clamp. We also determined the OGTT-derived ISI (glucose uptake/[mean plasma glucose × log mean plasma insulin]) advocated by Cederholm and Wibell (12) for comparison. We have referred to this as the ISI(Ceder). In the preceding equation, glucose uptake during the OGTT is estimated to be the difference between the oral glucose load and the glucose remaining in the glucose space as indicated by the difference between the FPG and 2-h plasma glucose concentrations. The glucose space was calculated as 0.19 × body weight. To adjust for the influence of different plasma glucose levels, the estimated glucose uptake rate was divided by the mean plasma glucose concentration from 0 to 120 min.

Recently, Belfiore et al. (10) proposed a new ISI that is a hyperbolic function of the product of the mean plasma glucose and insulin concentrations during the OGTT. This ISI yields a range of 0–2 and is calculated as follows:

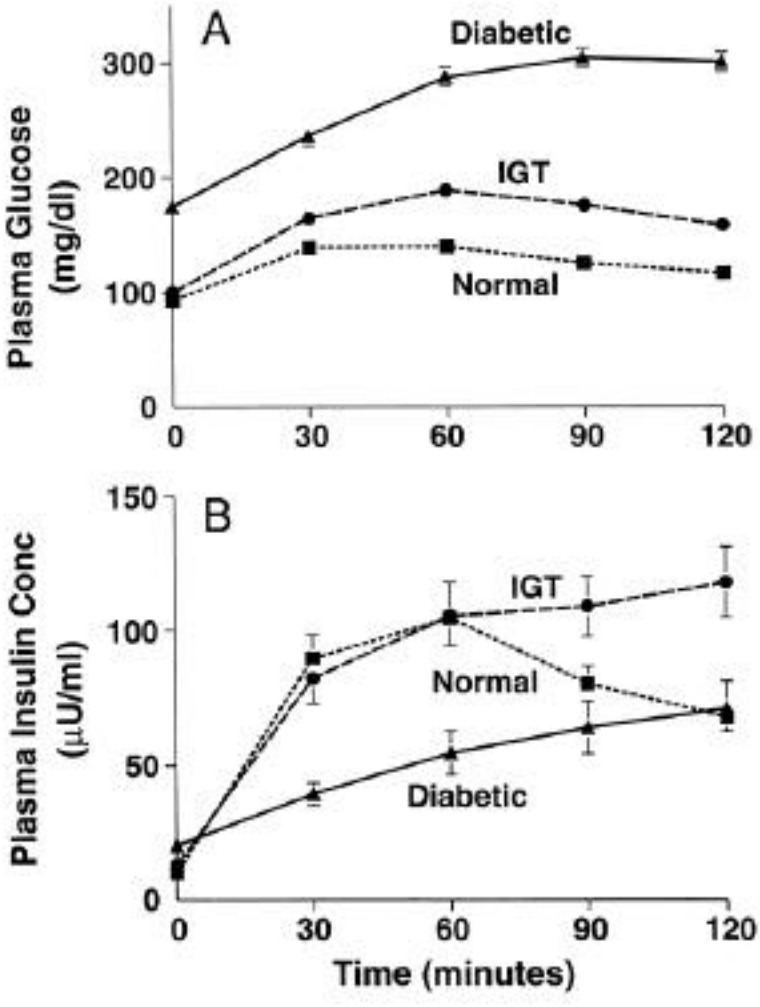

Figure 1—*Plasma glucose (A) and insulin (B) concentrations during an OGTT performed in subjects with normal glucose tolerance, IGT, and type 2 diabetes. Data are means ± SEM.*

$$\frac{2}{\left(\text{Mean OGTT glucose concentration} \times \left(\frac{\text{mean OGTT insulin concentration}}{C} + 1\right)\right)} \quad (5)$$

where C is a constant. We refer to this index as ISI(Bel).

All data are expressed as the mean ± SEM. Correlation analyses were performed with standard equations (StatView for Windows 5.0; SAS Institute, Cary, NC).

RESULTS

OGTT: Plasma glucose and insulin concentrations

The plasma glucose and insulin levels during the OGTT in control, IGT, and diabetic subjects are presented in Fig. 1. In IGT subjects, the plasma insulin concentrations at 30 and 60 min were similar to those in

Table 2—*Correlation matrix between indices of whole-body insulin sensitivity derived from the euglycemic insulin clamp and OGTT*

		$\frac{1{,}000}{EGP \times FPI}$	$\frac{R_d}{SSPI}$	$\frac{k}{FPI \times FPG}$	$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$
Hepatic sensitivity (tracer)	$\frac{1{,}000}{EGP \times FPI}$	1	—	—	—	—	—
Whole-body insulin sensitivity (insulin clamp)	$\frac{R_d}{SSPI}$	0.698	1	—	—	—	—
Insulin (hepatic) sensitivity (HOMA)	$\frac{k}{FPI \times FPG}$	0.668	0.691	1	—	—	—
Insulin sensitivity from OGTT							
Cederholm	$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	0.503	0.623	0.681	1	—	—
Belfiore	$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	0.472	0.543	0.512	0.538	1	—
Composite	$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$	0.670	0.732	0.920	0.737	0.763	1

There were 153 observations in this computation. Hepatic $\left[\frac{1{,}000}{EGP \times FPI}\right]$ and whole-body $\left[\frac{R_d}{SSPI}\right]$ insulin sensitivity during the euglycemic insulin clamp represent the standard against which the indices of hepatic $\left[ISI(HOMA) = \frac{k}{FPI \times FPG},\ k = 22.5 \times 18\right]$ and whole-body $\left[ISI(Ced) = \frac{Uptake}{\bar{G} \times \log \bar{I}},\ ISI(Bel) = \frac{2}{(\bar{G} \times \bar{I})/C + 1},\ ISI(composite) = \frac{10{,}000}{\sqrt{FPG \times FPI \times \bar{G} \times \bar{I}}}\right]$ insulin sensitivity during the OGTT are compared. C, constant value; $\bar{G}$, mean plasma glucose concentration during OGTT; $\bar{I}$, mean plasma insulin concentration during OGTT.

subjects with normal glucose tolerance, whereas the 90- and 120-min levels were increased. In type 2 diabetic subjects, the 30- and 60-min plasma insulin concentrations were significantly reduced compared with subjects with both normal glucose tolerance and IGT.

Hepatic insulin sensitivity

The inverse of the product of basal EGP (primarily hepatic) measured with 3-[^{3}H]glucose and the FPI concentration provides a direct measure of hepatic sensitivity to insulin under postabsorptive conditions. This measurement agrees reasonably well ($r = 0.69$, $P < 0.0001$) with the HOMA-derived measure (k/FPI × FPG) of hepatic insulin sensitivity (Table 2). The correlation was equally strong in subjects with normal glucose tolerance and type 2 diabetes.

Although the direct measure of hepatic insulin sensitivity (1,000/EGP × FPI) correlated well ($r = 0.70$, $P < 0.0001$) with the measurement of whole-body insulin sensitivity, the correlation is significantly less than unity. This results from the presence of a significant number of individuals with normal or near-normal hepatic sensitivity to insulin but impaired whole-body (primarily muscle) insulin sensitivity and vice versa (Fig. 2).

Whole-body insulin sensitivity

Whole-body insulin sensitivity measured with the euglycemic insulin clamp (R_d/SSPI) correlated closely ($r = 0.73$, $P < 0.0001$) with our proposed measurement of insulin sensitivity from the OGTT (Fig. 3). This correlation was most robust in subjects with normal glucose tolerance ($r = 0.73$, $P < 0.0001$) (Table 3) and in subjects with IGT ($r = 0.66$, $P < 0.0001$) (Table 4) and was somewhat weaker in type 2 diabetic individuals ($r = 0.54$, $P < 0.0001$) (Table 5). The lower correlation coefficient in diabetic patients most likely reflects the decline in insulin secretion in this group (Fig. 1). The ISI(HOMA) ($r = 0.69$, $P < 0.0001$), ISI(Ceder) ($r = 0.62$, $P < 0.0001$), and ISI(Bel) ($r = 0.54$, $P < 0.0001$) estimates of whole-body insulin sensitivity yielded correlation coefficients (compared with the insulin clamp) that were somewhat lower than the estimate derived from the method that we have proposed. The correlation coefficients derived from the Cederholm ($P < 0.05$) and Belfiore ($P < 0.01$) estimates were significantly less than the one we propose. There was no correlation between the G/I ratio during the OGTT and the measure of insulin sensitivity from the insulin clamp ($r = -0.02$, NS).

CONCLUSIONS — Insulin resistance is a common metabolic abnormality that characterizes individuals with various medical disorders, including type 2 diabetes (1,3,31,32) and obesity (33). Insulin resistance is present in approximately 20–25%

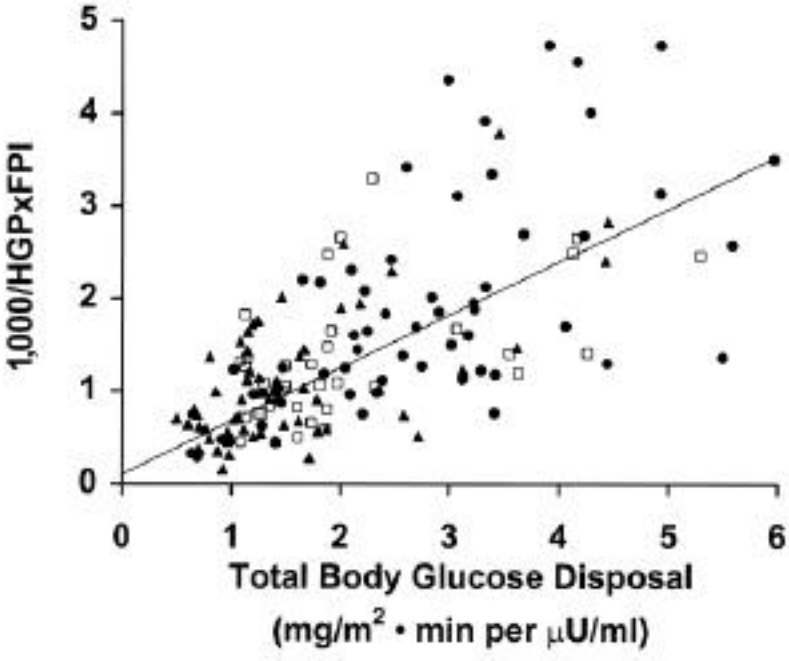

Figure 2—*Relationship between hepatic insulin sensitivity (1,000/HGP × FPI) and whole-body insulin sensitivity (Rd/SSPI). Although a reasonably good correlation (r = 0.70, P < 0.001) between these variables exists, there are a significant number of individuals with normal or near-normal hepatic insulin sensitivity but impaired whole-body (primarily muscle) insulin sensitivity and vice versa.*

of the nondiabetic population and occurs in association with many cardiovascular and metabolic abnormalities (e.g., hypertension, dyslipidemia, atherosclerotic cardiovascular disease, central obesity, IGT, microalbuminuria, and elevated plasminogen activator inhibitor-1). This constellation of disorders has collectively been referred to as the insulin resistance syndrome (34,35). Because impaired insulin action is an underlying feature of these commonly encountered clinical disorders, there has been widespread interest in the development of techniques to assess insulin sensitivity in humans in vivo (5). The euglycemic insulin clamp technique generally is considered to represent the most definitive method to quantitate whole-body insulin sensitivity in humans (2). When used in combination with radiolabeled glucose, the insulin clamp allows one to quantify the individual contributions of hepatic and peripheral (primarily muscle) insulin sensitivity to whole-body insulin-mediated glucose metabolism (3,31,32). In this study, we describe a simple method to provide indices of hepatic and whole-body insulin sensitivity from measurements of plasma glucose and insulin concentrations during the OGTT and have compared these ISIs with those derived from the euglycemic insulin clamp technique. Subjects who participated in the study had a range of glucose tolerance that varied from normal glucose tolerance to IGT to overt diabetes.

Many authors have noted that the diagnosis of diabetes can vary by as much as 15–20%, depending on whether one uses the FPG concentration (≥126 mg/dl) or the 2-h plasma glucose concentration (≥200 mg/dl) during the OGTT (36,37) as the diagnostic criteria. We believe that this variability represents the contribution of different metabolic and genetic abnormalities to the development of glucose intolerance in individuals with type 2 diabetes. Thus, some type 2 diabetic individuals have a predominant defect in hepatic insulin sensitivity and present with an excessive basal rate of HGP and fasting hyperglycemia, whereas others have a more pronounced disturbance in peripheral (primarily muscle) sensitivity to insulin and present with postmeal glucose intolerance. This is clearly demonstrated in Fig. 2, where one can identify individuals with hepatic insulin resistance and normal or near-normal glucose tolerance and vice versa. The ability to more precisely phenotype patients with type 2 diabetes may enhance our ability to identify genes responsible for the development of type 2 diabetes in humans (38). The observation that hepatic and peripheral insulin sensitivity can differ considerably in the same individual also raises concern about the use of the HOMA technique to provide a measure of in vivo insulin sensitivity (17–19) because an assumption of this model is that hepatic and peripheral insulin sensitivity are equivalent. Moreover, there are several other major assumptions in the

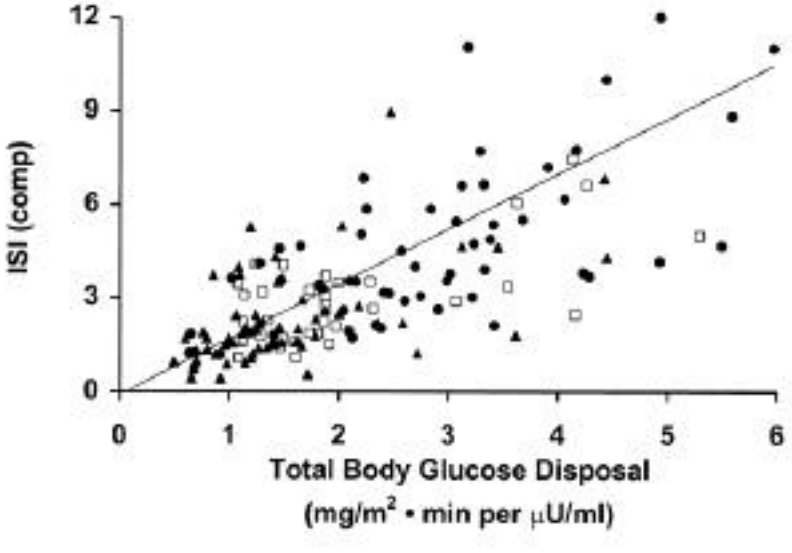

Figure 3—*Comparison of the proposed ISI during the OGTT [ISI(composite)] and the rate of insulin-mediated glucose disposal during the euglycemic insulin clamp (r = 0.73, P < 0.0001).*

Table 3—*Correlation matrix between indices of insulin sensitivity derived from the euglycemic insulin clamp and OGTT in subjects with normal glucose tolerance*

	$\frac{1{,}000}{EGP \times FPI}$	$\frac{R_d}{SSPI}$	$\frac{k}{FPI \times FPG}$	$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$
$\frac{1{,}000}{EGP \times FPI}$	1	—	—	—	—	—
$\frac{R_d}{SSPI}$	0.684	1	—	—	—	—
$\frac{k}{FPI \times FPG}$	0.633	0.654	1	—	—	—
$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	0.318	0.523	0.503	1	—	—
$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	0.479	0.654	0.659	0.849	1	—
$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$	0.613	0.727	0.935	0.709	0.852	1

See footnote for Table 2.

HOMA technique that are not likely to be correct (5). Nonetheless, despite this concern, we observed a good correlation between the ISI(HOMA) and that measured directly from the insulin clamp. The positive correlation between the ISI(HOMA) and that measured with the insulin clamp is not surprising because our results demonstrate that hepatic and muscle sensitivity to insulin are reasonably correlated. However, from a pathophysiological standpoint, in any given individual, the ISI(HOMA) (primarily liver) and the new composite index (muscle plus liver) provide different information. In a recent publication, Bonora et al. (39) reported an excellent correlation ($r = 0.79$, $P < 0.0001$) between HOMA and insulin clamp-derived measures of insulin sensitivity. It should be noted, however, that the investigators (39) used an insulin infusion rate of 20 mU · m^{-2} · min^{-1}, which would cause an incomplete suppression of HGP and a much smaller stimulation of peripheral (muscle) glucose uptake. These differences may explain the higher correlation between HOMA-derived and insulin clamp-derived measures of insulin

Table 4—*Correlation matrix between indices of insulin sensitivity derived from the euglycemic insulin clamp and OGTT in subjects with IGT*

	$\frac{1{,}000}{EGP \times FPI}$	$\frac{R_d}{SSPI}$	$\frac{k}{FPI \times FPG}$	$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$
$\frac{1{,}000}{EGP \times FPI}$	1	—	—	—	—	—
$\frac{R_d}{SSPI}$	0.52	1	—	—	—	—
$\frac{k}{FPI \times FPG}$	0.352	0.558	1	—	—	—
$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	0.304	0.481	0.455	1	—	—
$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	0.409	0.541	0.485	0.861	1	—
$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$	0.435	0.663	0.831	0.81	0.836	1

See footnote for Table 2.

Table 5—*Correlation matrix between indices of insulin sensitivity derived from the euglycemic insulin clamp and OGTT in subjects with type 2 diabetes*

	$\frac{1{,}000}{EGP \times FPI}$	$\frac{R_d}{SSPI}$	$\frac{k}{FPI \times FPG}$	$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$
$\frac{1{,}000}{EGP \times FPI}$	1	—	—	—	—	—
$\frac{R_d}{SSPI}$	0.623	1	—	—	—	—
$\frac{k}{FPI \times FPG}$	0.634	0.511	1	—	—	—
$\frac{Uptake}{\bar{G} \times \log \bar{I}}$	0.535	0.395	0.641	1	—	—
$\frac{2}{(\bar{G} \times \bar{I})/C + 1}$	0.55	0.481	0.541	0.691	1	—
$\frac{10{,}000}{\sqrt{(FPG \times FPI) \times (\bar{G} \times \bar{I})}}$	0.669	0.544	0.898	0.751	0.806	1

See footnote for Table 2.

sensitivity in Bonora et al.'s study (39) and our study. Other investigators have reported a poor correlation between the measures of insulin sensitivity obtained from HOMA and the euglycemic insulin clamp (20).

Several large studies have shown that the minimal model technique provides correlation coefficients of only 0.5–0.6 when compared with the euglycemic insulin clamp (40–42), and the limitations of the minimal model technique recently have been reviewed (43). When compared with the euglycemic insulin clamp, the insulin suppression test provides correlation coefficients (r = 0.8–0.9) that are higher than those calculated from the minimal model (44). This is not surprising because the insulin suppression test basically is an insulin clamp study performed at hyperglycemic (diabetic) or near-normoglycemic (nondiabetic) levels.

Because of its precision in quantitating insulin sensitivity under physiological conditions of insulinemia and glycemia, and because it can easily be combined with other methods (e.g., tracer glucose infusion, indirect calorimetry, limb balance), the euglycemic insulin clamp remains the preferred technique to evaluate the contribution of impaired insulin sensitivity to overall glucose homeostasis (5). However, the OGTT remains the most commonly performed test to examine glucose tolerance. Although many authors have proposed the use of the G/I ratio (absolute or incremental) as an index of insulin sensitivity (15,16), no one has correlated the G/I ratio during the OGTT with the direct measurement of insulin sensitivity with the euglycemic insulin clamp. In 153 subjects who received both an OGTT and an insulin clamp, we found no correlation (r = −0.02, NS) between the G/I ratio during the OGTT and the measurement of insulin sensitivity during the insulin clamp. One could argue that this poor correlation results from the fact that the OGTT

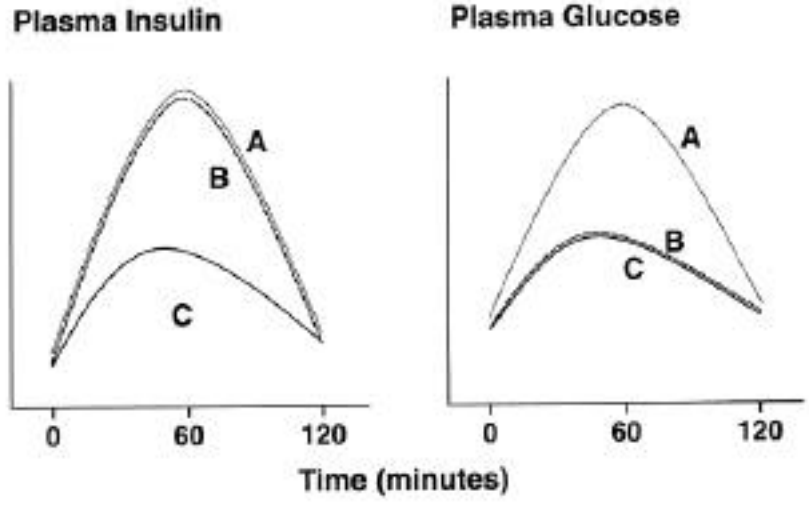

Figure 4—*Use of the plasma G/I ratio during the OGTT to provide an index of insulin sensitivity. Subjects B and C have the same plasma glucose profile, but subject B requires twice as much insulin to maintain normoglycemia. It follows, therefore, that subject B must be resistant to insulin and have a lower (by 50%) G/I ratio. Subject A produces an amount of insulin that is identical to that of subject B but has a plasma glucose curve that is much higher than that of subject B. According to the previous line of reasoning, subject A should be more resistant than subject B (i.e., he should have a lower G/I ratio), but the opposite is true.*

measures both glucose effectiveness and insulin sensitivity, whereas the insulin clamp measures only the latter. However, the indices of insulin sensitivity derived from the euglycemic insulin clamp and the hyperglycemic clamp agree closely (2). The fallacy in the use of the G/I ratio as an index of insulin sensitivity is obvious from the three OGTTs presented in Fig. 4. Subject B and subject C have the same plasma glucose profile, but subject B requires twice as much insulin to maintain normoglycemia. It follows, therefore, that subject B must be resistant to insulin and have a lower (by 50%) G/I ratio. Subject A produces an amount of insulin that is identical to that of subject B but has a plasma glucose curve that is much higher than that of subject B. According to the previous line of reasoning, subject A should be more resistant than subject B (i.e., he should have a lower G/I ratio), but the opposite is true. This simple case analysis illustrates the problems inherent in the use of the G/I ratio to provide an index of insulin sensitivity.

Some investigators have advocated the use of the product of the plasma glucose and insulin concentrations during the OGTT as an index of whole-body insulin sensitivity (6,7). Intuitively, this formula makes more sense. A high plasma insulin concentration in the presence of a normal or increased plasma glucose concentration indicates the presence of insulin resistance. Moreover, the higher the plasma insulin response and the higher the plasma glucose level, the more severe must be the state of insulin resistance. It is evident from Fig. 4 that the product of the plasma glucose and insulin concentrations (not the G/I ratio) provides the better index of insulin sensitivity. The lower the (glucose × insulin) product, the more sensitive are the tissues of the body to insulin. Nonetheless, a rigorous test of this hypothesis has yet to be carried out. Therefore, we compared the glucose × insulin index of insulin sensitivity (1/(glucose × insulin)) during the OGTT with the rate of insulin-mediated glucose disposal during the euglycemic insulin clamp. These two indices were reasonably well correlated ($r = 0.56$, $P < 0.0001$). Glucose uptake from the plasma compartment divided by the product of the plasma glucose and insulin (or log insulin) concentrations also has been suggested as an index of insulin sensitivity (11,12). In our study, this index of whole-body insulin sensitivity, which represents the combined effect of insulin to stimulate peripheral glucose uptake and to suppress EGP, correlated well ($r = 0.62$, $P < 0.0001$) with the rate of insulin-mediated glucose disposal during the euglycemic insulin clamp. The index of insulin sensitivity proposed by Belfiore et al. (10) correlated least well with the insulin clamp results (Table 2). By using the data available from the OGTT, we have developed a new index (Eq. 4) of whole-body insulin sensitivity that represents a composite of hepatic and peripheral tissues and considers insulin sensitivity in the basal state (FPG × FPI) and after the ingestion of a glucose load (mean plasma insulin × mean plasma glucose). This index correlated strongly ($r = 0.73$, $P < 0.0001$) with the direct measure of insulin sensitivity derived from the euglycemic insulin clamp. In fact, this correlation is higher than that provided by the minimal model technique (40–42). Because an OGTT is routinely performed in most metabolic and epidemiological studies, an easily calculated index of whole-body insulin sensitivity (Eq. 4) is readily available and can be used to rank individuals according to the ability of their tissues to respond to insulin. Because this index is more robust than that provided by the minimal model technique, and because the OGTT also provides an index of insulin secretion (20,45), we suggest that the OGTT can be used effectively to define insulin sensitivity and secretory defects in individuals with impaired glucose homeostasis.

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