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Insulin Sensitivity from Meal Tolerance Tests in Normal Subjects: A Minimal Model Index

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ABSTRACT

In this report a new approach is introduced that allows estimation of insulin sensitivity (S_I) from orally ingested glucose during an oral glucose tolerance test (OGTT) or a meal glucose tolerance test (MGTT) in normal subjects. The method hinges on the classic minimal model of glucose kinetics that is coupled with an equation describing the rate of appearance of glucose into the circulation after oral glucose ingestion. The model provides an estimate of S_I in a given individual based on simple area under the curve type of calculations. To prove the reliability of the new approach, MGTT studies performed in 10 normal subjects were analyzed and the S_I index from the MGTT was compared with the S_I index obtained in the same subjects from an insulin-modified, frequently sampled iv glucose test (FSIGT). S_I from the MGTT was $13.6 \pm 3.9 \times 10^{-4}$ dL/kg·min/μU·mL and was strongly correlated to the S_I from the FSIGT ($r_s = 0.89$; $P < 0.01$). In conclusion, this study shows that in normal subjects the minimal model can be applied to a MGTT/OGTT to derive an index of insulin sensitivity that is in good agreement with the one estimated from the FSIGT. Due to its simplicity, this method has potential for use in population studies, but further investigation is required to ascertain its applicability to subjects with severe insulin resistance and impaired secretory function. (*J Clin Endocrinol Metab* **85:** 4396–4402, 2000)

INSULIN RESISTANCE plays a pivotal role in the pathophysiology of diabetes and has been associated with obesity, cardiovascular disease, hypertension, and cancer (1–3). In fact, insulin resistance has been shown to be a risk factor for several of these conditions. Although excellent methods exist for quantitative assessment of insulin sensitivity in the laboratory setting (4), accurate measurement in studies of more than a few subjects has proven problematic. Although fasting insulin has been used as a surrogate for insulin resistance, it bears a nonlinear relationship to insulin action directly measured (5) and fails when there is even subtle β-cell failure. More direct, but complex, techniques have employed administration by vein of insulin and/or glucose. Given the difficulty of venous administration, it would appear highly desirable to obtain an accurate measure of insulin sensitivity from oral administration alone. Unfortunately, such methods have not been forthcoming because of the difficulties of estimating the appearance in the systemic circulation of nutrient taken by mouth and absorbed from the gastrointestinal tract.

Nevertheless, due to the possible importance of an oral methodology, in this manuscript we examine the feasibility of measuring insulin sensitivity from an oral meal. To do this, we have coupled the classic minimal model of glucose kinetics (6) with a simple mathematical description of glucose absorption from the gastrointestinal tract. To examine the reliability of the meal-based index of insulin sensitivity, $S_{I(oral)}$, this parameter was compared with the insulin sensitivity index estimated from the insulin-modified frequently sampled iv glucose test (FSIGT) (7) measured in the same subjects.

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Subjects and Methods

Subjects and experimental protocol

The data used in the current study, provided by Dr. David Owens, are part of a published study (8) to which we refer for further details. Briefly, 10 healthy subjects (4 men and 6 women; age, 47.7 ± 2.6 yr; body mass index, 25.9 ± 1.2 kg/m^2) with normal glucose tolerance received on different occasions an insulin-modified FSIGT or a meal tolerance test (MGTT). Both tests were performed in the morning after a 10-h overnight fast.

The insulin-modified FSIGT consisted of a 300 mg/kg glucose bolus at time zero, followed by an insulin injection of 0.03 U/kg at 20 min, as previously described (7). Blood was sampled at −30, −15, −1, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min.

The meal was mainly solid, with a small amount of juice and milk. It consisted of 15 g Weetabix, 10 g skimmed milk, 250 mL pineapple juice, 50 g white meat chicken, 60 g wholemeal bread, and 10 g polyunsaturated margarine. The total energy was 482 Cal; the total carbohydrate was approximately 75 g. The meal was eaten within 10 min. Blood samples were collected at −30, −1, 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, and 240 min.

Analytical techniques

The plasma glucose concentration was measured by a glucose oxidase method. Immunoreactive insulin was measured in both tests by a conventional RIA method (antibody M8309 from Novo-Nordisk, Bagsvaerd, Denmark).

Data analysis

The analysis of both the FSIGT and the MGTT studies exploits the classic minimal model (6). Whereas during the FSIGT glucose enters the systemic circulation directly, during the MGTT food is ingested, and nutrients, including glucose, encounter the systemic circulation only after absorption from the gastrointestinal tract and passage through the

liver (see Fig. 1). Making explicit the appearance of exogenous glucose into the minimal model yields:

$$\begin{aligned} \dot{g}(t) &= -[p_1 + x(t)]g(t) + p_1 g_b + \frac{r_a(t)}{V}; \quad g(0) = g_b \\ \dot{x}(t) &= -p_2 x(t) + p_3[i(t) - i_b]; \qquad x(0) = 0 \end{aligned} \tag{I}$$

where r_a is the generic expression for the rate of entry of exogenous glucose into the systemic circulation per unit BW (milligrams per kg/min). During the FSIGT, r_a coincides with the impulse injection of a glucose dose D (milligrams per kg), *i.e.* $r_a(\text{FSIGT}) = D\delta(t)$; during the MGTT/OGTT, r_a coincides with the rate of absorbed glucose, *i.e.* $r_a(\text{MGTT/OGTT}) = Ra_{ABS}(t)$, where Ra_{ABS} is defined as the posthepatic appearance of newly absorbed glucose.

Most model variables/parameters were previously described (6); g is the plasma glucose concentration (milligrams per dL), with g_b denoting its basal value, × is insulin action (minutes^{-1}) exerted on glucose disposal from an insulin compartment remote from plasma, i is the plasma insulin concentration (microunits per mL), with i_b denoting its basal value, V is the glucose distribution volume per unit BW (milliliters per kg), p_2 (minutes^{-1}) governs the speed of rise and decay of insulin action, and p_3 (minutes^{-2} per μU/mL) governs its size.

Insulin sensitivity from the FSIGT

The minimal model parameters p_1, p_2, p_3, and V were estimated by weighted nonlinear least squares from glucose and insulin data collected during an insulin-modified FSIGT as previously described (9). As is usual, measurements from the first 8 min after iv glucose were ignored in model identification. The insulin sensitivity index, $S_{I(\text{FSIGT})}$ (milliliters per kg/min·μU/mL), was calculated as:

$$S_{I(FSIGT)} = \frac{p_3}{p_2} V = S_I V \tag{II}$$

$S_{I(\text{FSIGT})}$ is thus the minimal model fractional (*i.e.* per unit volume) index, S_I, multiplied by the minimal model estimate of the glucose distribution volume, V. So defined, $S_{I(\text{FSIGT})}$ has the same units of the analogous clamp index (10) and of the $S_{I(\text{oral})}$ index derived as described below.

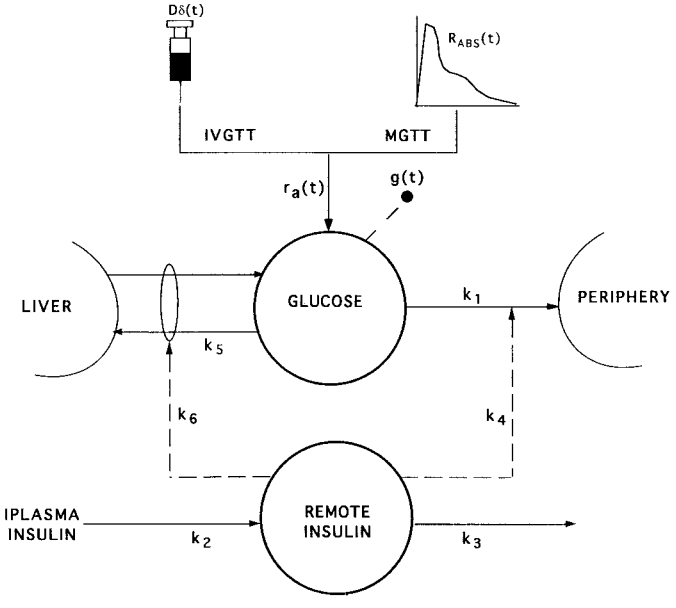

FIG. 1. Diagram of the minimal model used to interpret the insulin-modified FSIGT and the MGTT/OGTT. The glucose mass input to the model, $r_a(t)$, is the impulsive dose of glucose, $D\delta(t)$, for the FSIGT, or the rate of appearance of absorbed glucose, $Ra_{ABS}(t)$, for the MGTT/OGTT.

Insulin sensitivity from the MGTT

The challenge in using the minimal model to analyze oral MGTT/OGTT data is to describe mathematically how exogenous glucose reaches the systemic circulation. We made the assumption that the profile of Ra_{ABS} resembles an anticipated version of glucose excursion above basal, $\Delta g(t) = g(t) - g_b$. Following the principle of parsimony, we used a simple parsimonious parametric representation for describing the relationship between Ra_{ABS} and Δg:

$$\Delta\dot{g}(t) = -a\Delta g(t) + bRa_{ABS}(t) \tag{III}$$

where a is a parameter governing the delay and smoothness of Δg with respect to Ra_{ABS}, and b is a scale factor. Initially we assumed Δg (≥ 0) during the test; subsequently, we generalized the analysis by allowing glucose to take on values below its basal level late during the test.

Substituting the expression for Ra_{ABS} given by Eq III into the minimal model equations yields

$$\begin{aligned} \dot{g}(t) &= -[p_1 + x(t)]g(t) + p_1 g_b + \frac{[a\Delta g(t) + \Delta\dot{g}(t)]}{bV}; \quad g(0) = g_b \\ \dot{x}(t) &= -p_2 x(t) + p_3[i(t) - i_b]; \qquad x(0) = 0 \end{aligned} \tag{IV}$$

By integrating the minimal model equation describing insulin action (11, 12), the following expression for insulin sensitivity during an oral test is obtained:

$$S_{I(oral)} = \frac{p_3}{p_2} V = \frac{\int_0^\infty x(t)dt}{\int_0^\infty [i(t) - i_b]dt} V \tag{V}$$

Thus, what remains to be determined is the integral of x(t), the time course of insulin action during the test. The resulting expression for $S_{I(\text{oral})}$ (milliliter per kg/min·μU/mL) is the following (see details in *Appendix*):

$$S_{I(oral)} = \frac{f \cdot D_{oral} \dfrac{AUC[\Delta g(t)/g(t)]}{AUC[\Delta g(t)]} - GE \cdot AUC[\Delta g(t)/g(t)]}{AUC[\Delta i(t)]} \tag{VI}$$

where AUC denotes the area under the curve calculated from time zero to the end of the test, $GE = p_1 V$ is glucose effectiveness (milliliters per kg/min), D_{oral} is the dose of ingested glucose per unit of body weight (milligrams per kg), and f is the fraction of ingested glucose that actually appears in the systemic circulation (*i.e.* survives gastrointestinal absorption and one-pass hepatic uptake).

When the glucose concentration falls below the basal level during the test, the equation for insulin sensitivity becomes

$$S_{I(oral)} = \frac{f \cdot D_{oral} \dfrac{AUC[\Delta g(t)/g(t)]_0^{t_0} - AUC[\Delta g(t)/g(t)]_{t_0}^{\infty}}{AUC[\Delta g(t)]_0^{t_0} - AUC[\Delta g(t)]_{t_0}^{\infty}} - GE \cdot AUC[\Delta g(t)/g(t)]}{AUC[\Delta i(t)]} \tag{VII}$$

The AUC of $\Delta g/g$ and Δg are separately calculated in the intervals $0\text{-}t_0$ and $t_0\text{-}\infty$, and the negative AUC calculated in the interval $t_0\text{-}\infty$ is subtracted from the positive AUC calculated in the interval $0\text{-}t_0$.

Calculation of $S_{I(\text{oral})}$ with Eq VI and VII requires the investigator to insert values for GE and f. Generally, individual estimates of GE and f are not available. Therefore, mean values derived from the literature must be used. In the present study GE was fixed at 0.024 dL/kg·min, *i.e.* the mean value of glucose effectiveness in normal subjects reported in the review by Best *et al.* (13). Estimates of f, fraction of glucose taken orally to appear in the systemic circulation during an OGTT, vary between 70–100% (14) (see *Discussion*). In a previous study (15) we estimated that after a mixed meal the average absorption of oral glucose was

80% (n = 7; range, 67–95%). We thus set f = 0.8 in the formulas used to calculate $S_{I(oral)}$.

It is worth noting that evaluation of $S_{I(oral)}$ requires that the AUCs are calculated from the beginning of the test (time zero) until the glucose system returns to the pretest steady state. In the present study, insulin sensitivity values were calculated over the interval 0–240 min (see *Discussion*), and AUCs were computed using the trapezoidal rule.

Sensitivity analysis

Because values of glucose effectiveness, GE, and fractional splanchnic absorption of oral glucose, f, are assumed in this method, we examined the dependence of calculated $S_{I(oral)}$ upon the assumed values of GE and f. A sensitivity analysis was performed in which we evaluated how the estimate of $S_{I(oral)}$ changes in relation to a ±50% change in glucose effectiveness (assuming GE between 0.036 and 0.012 dL/kg·min) and in relation to a ±20% change in the absorption of oral glucose (assuming f between 0.96–0.64).

The impact of a shorter duration of the MGTT (180 instead of 240 min) and of a reduction of the sampling frequency (one sample every 30 min) on the estimation of $S_{I(oral)}$ was also evaluated by calculating $S_{I(oral)}$ from the glucose and insulin data measured at −30, −1, 30, 60, 90, 120, 150, and 180 min.

Statistical analysis

Results are given as the mean ± SEM. Due to the presence of a subject who was very sensitive to insulin, the distributions of $S_{I(FSIGT)}$ and $S_{I(oral)}$ were not normal. We thus used the Wilcoxon signed rank test to evaluate differences between $S_{I(FSIGT)}$ and $S_{I(oral)}$, and Spearman's rank correlation coefficient (r_s) to examine the strength of the association between them.

Results

Mean plasma glucose and insulin concentrations during the insulin-modified FSIGT and during the MGTT are shown in Fig. 2. Of note is that by the end of the MGTT at 240 min, glucose and insulin had both virtually returned to their respective pretest levels. Of course, this does not prove that all oral glucose had been absorbed or that the metabolism of oral glucose was complete (see *Discussion*).

The FSIGT-based estimate of fractional insulin sensitivity, S_I; the minimal model volume of glucose distribution, V; and the insulin sensitivity, $S_{I(FSIGT)} = S_I \times V$, together with the MGTT-based estimate of insulin sensitivity, $S_{I(oral)}$, are listed in Table 1 for the 10 subjects. $S_{I(oral)}$ was strongly correlated with $S_{I(FSIGT)}$ ($r_s = 0.89$; $P < 0.01$; see Fig. 3). Despite the strong correlative relationship between the tests, the absolute values of $S_{I(oral)}$ and $S_{I(FSIGT)}$ were significantly different from each other, with the value from the oral test being about twice that from the iv test (13.6 ± 3.9 *vs.* $6.2 \pm 1.3 \times 10^{-4}$ dL/kg·min/μU·mL; $P < 0.01$). When calculation of $S_{I(oral)}$ was performed relying on a reduced sampling schedule of only eight glucose and insulin samples collected between 0–180 min, results were virtually the same; $S_{I(oral)}$ was $12.9 \pm 3.5 \times 10^{-4}$ dL/kg·min/μU·mL and remained very well correlated with $S_{I(FSIGT)}$ ($r_s = 0.90$; $P < 0.01$). Of note is that accuracy was maintained in individual subjects, as demonstrated by the strong correlation between the two $S_{I(oral)}$ estimates obtained

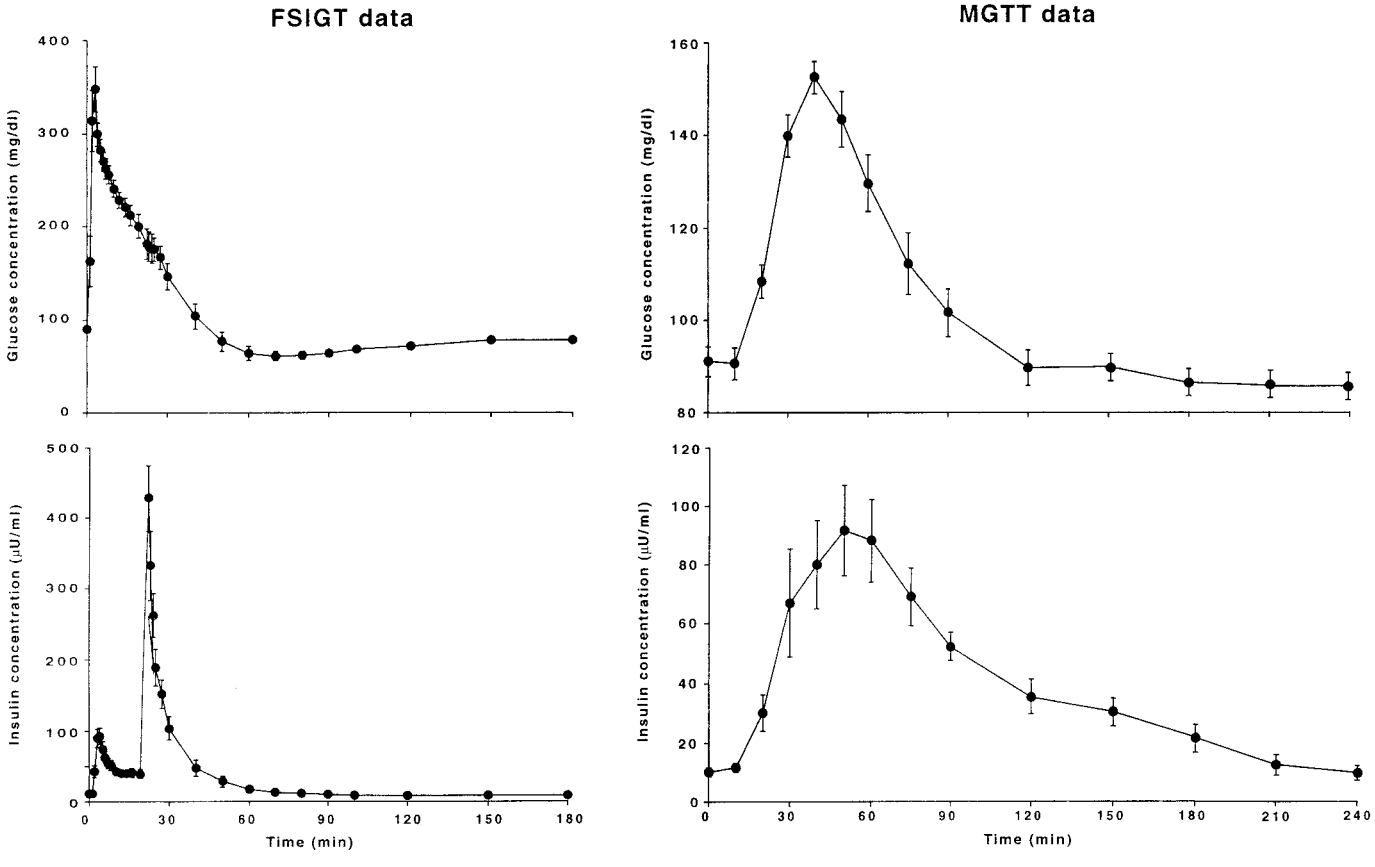

FIG. 2. Average concentrations of glucose and insulin during the insulin-modified FSIGT and the MGTT in normal subjects (mean ± SEM; n = 10).

TABLE 1. Intravenous- and oral-based estimates of insulin sensitivity

Subject no.	S_1 (10^{-4} min/μU·mL)	V (dL/kg)	$S_{1(FSIGT)}$ (10^{-4} dL/kg·min/μU·mL)	$S_{1(oral)}$ (10^{-4} dL/kg·min/μU·mL)
1	3.3	1.7	5.5	7.6
2	3.2	1.4	4.5	13.3
3	3.5	1.5	5.0	9.0
4	10.9	1.4	15.8	46.8
5	1.5	1.2	1.8	4.2
6	3.2	1.3	4.0	6.6
7	4.2	1.5	6.1	17.8
8	2.0	1.2	2.3	6.8
9	8.7	1.3	11.4	13.7
10	4.5	1.3	5.8	9.6
Mean ± SEM	4.5 ± 0.9	1.4 ± 0.1	6.2 ± 1.34	13.6[a] ± 3.9

[a] $P < 0.01$ *vs.* $S_{1(FSIGT)}$, by Wilcoxon signed rank test.

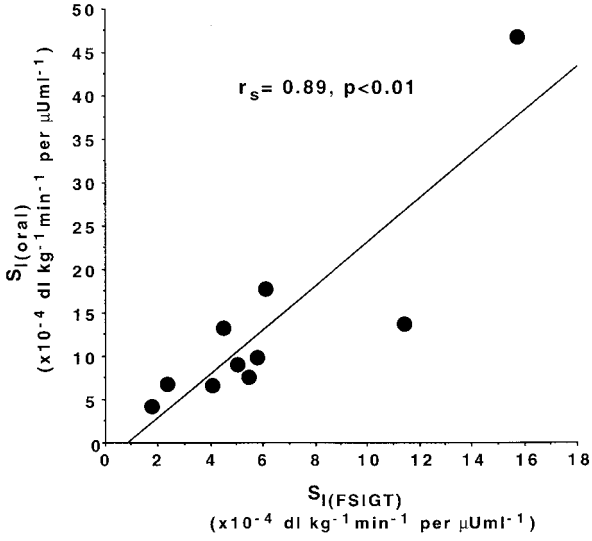

FIG. 3. The relation between $S_{I(oral)}$ and $S_{I(FSIGT)}$ in 10 normal subjects. The degree of association between $S_{I(oral)}$ and $S_{I(FSIGT)}$ was assessed using the nonparametric Spearman's method due to the presence of a subject (no. 4 in Table 1) whose insulin sensitivity was much higher than the others. When the correlation analysis was repeated without this subject, Pearson's r was 0.63 ($P = 0.068$).

from the full and the reduced sampling schedule ($r_s = 0.99$; $P < 0.01$).

The results of the sensitivity analysis indicated that in these normal subjects calculation of $S_{I(oral)}$ is little influenced by changes in the value of glucose effectiveness. A ±50% change in GE (range, 0.012–0.036 dL/kg·min) produced only a ±2.3% change in $S_{I(oral)}$ (range, 13.9–13.3 × 10^{-4} dL/kg·min/μU·mL). In contrast to its little dependence upon glucose effectiveness, in these normal subjects the value of $S_{I(oral)}$ was quite sensitive to changes in f; a ±20% change in f (range, 0:96–0.64) produced a ±21% change in $S_{I(oral)}$ (range, 16.4–10.7 × 10^{-4} dL/kg·min/μU·mL).

Discussion

Overwhelming interest in insulin resistance as a risk factor for chronic disease is reflected in the widespread application of the minimal model methodology to large population groups. For example, the method was applied to 1524 subjects in the Insulin Resistance and Atherosclerosis Study (16), and those tests have been repeated in a follow-up study. The method was also used in population genetics studies such as FUSION, in which minimal model parameters, including insulin sensitivity, S_I, are tested for linkage with markers on the human genome (17). Obviously, complex laboratory approaches are not applicable to a proliferating number of large studies; on the contrary, the iv injection of glucose and insulin is a challenge that entails cost and labor, and it would be useful if they could be avoided.

It would be beneficial if the simpler oral route of glucose administration could be the basis upon which S_I were calculated. In the present work we have developed the theoretical framework for such a methodology. This approach was originally rejected because of the need to estimate the rate of entry of orally taken glucose into the systemic circulation. However, at that time we were most concerned with studies using small numbers of subjects in which iv administration was feasible and not prohibitively costly. However, the accelerating rate of appearance of large studies encouraged us to reexamine this methodology.

In the present study we introduce a new approach that exploits the minimal model, but adds a parsimonious parametric representation of splanchnic glucose absorption that allows the measurement of insulin sensitivity in each individual from an AUC type of calculation. Obviously such a calculation is simpler to perform than the nonlinear estimation procedure required for the iv method (6, 18).

We have examined this new approach to derive estimates of insulin sensitivity from meal glucose tolerance data in 10 subjects with normal glucose tolerance. Comparing the S_I index obtained with this approach with the insulin-modified iv test by correlation analysis revealed a strong and highly significant correlation between the S_I index measured in the two experiments ($r_s = 0.89$; $P < 0.01$). This result suggests that both methods are measuring similar physiological phenomena, most likely the sum effects of insulin to enhance glucose uptake by peripheral tissues (mostly muscle) and concomitantly suppress liver glucose output. The present results are reminiscent of the linear relationship between results from the minimal model and the euglycemic glucose clamp method (10). Thus, it can be argued that the meal tolerance test (and presumably the oral glucose tolerance test) can be used, along with Eq VI and VII above, to yield an acceptable index of insulin sensitivity in normal individuals.

One striking result from the present study is that although one might predict a one to one concordance between the FSIGT and MGTT estimates of S_I because they both rely on

the minimal model and have the same units, we found that $S_{I(oral)}$ was numerically twice as great as $S_{I(FSIGT)}$ (13.6 *vs.* 6.2×10^{-4} dL/kg·min/μU·mL). Several explanations for this unexpected result may be suggested. One possibility is that the way Ra_{ABS} is depicted in the model is not sufficiently accurate. To allow derivation of S_I from MGTT/OGTT data, we resorted to a simple parametric description based on the idea that Ra_{ABS} is an anticipated version of glucose excursion above basal. The question of whether this description is too simplistic needs to be addressed by future studies in which the time course of Ra_{ABS} will be accurately assessed with the appropriate modeling and experimental techniques (such as the specific activity clamp). However, we speculate that the high degree of association between $S_{I(FSIGT)}$ and $S_{I(oral)}$ makes it unlikely that the description of Ra_{ABS} is affected by gross errors. Another possibility is related to the fact that with this method one is forced to estimate the fraction of glucose taken by mouth that appears in the vena cava, emanating from the liver. There are several reasons why f, which was assigned a value of 0.8, may have been overestimated in this study. First, we assumed that gastrointestinal absorption of glucose is finished by 240 min. This was done for convenience, because the database used herein included a 240-min meal tolerance test. However, in a mixed meal tolerance test, absorption of nutrients is much slower than with a carbohydrate meal. Certain peptide hormones, such as glucagon-like peptide-1 (GLP-1), act as brakes on motility and may well slow the movement of ingested carbohydrate down the gastrointestinal tract. We can expect that this phenomenon would be less of a problem with an OGTT, because the so-called brake peptides are released with intake of fat. However, the value of 0.8 for f is not without foundation. In a previous MGTT study (15) in which f was estimated, particular care was employed in terms of frequency of blood sampling, duration of the experiment, and modeling analysis. Of course, we cannot exclude that in the present MGTT study f was lower than 0.8 (in the literature there are studies reporting values of f as low as 0.7 for the OGTT). Thus, further careful examination of fractional absorption of orally administered glucose is justified to determine the external value of f that should be used with the present new methodology. An additional caveat is that there may well be differences in f for different states, particularly in patients with diabetes, in whom neuropathy may alter gastrointestinal function.

Despite these considerations, it is possible that the outcome of $S_{I(oral)} > S_{I(FSIGT)}$ is not due solely to an overestimation of f. In fact, as shown by the sensitivity analysis, even with f reduced to 0.64, $S_{I(oral)}$ is reduced only to 10.7×10^{-4} dL/kg·min/μU·mL, still higher than $S_{I(FSIGT)}$. In this regard it is important to remember that the minimal model is based upon a single compartment simplification of glucose distribution. It has been shown that this simplification causes difficulties in accounting for the rapid changes in glucose concentration experienced after an iv glucose injection (11, 12, 19). In contrast, it is likely that when glucose and insulin change more slowly, such as during a MGTT or an OGTT, a single compartment representation is sufficiently adequate (20). Whether the single compartment simplification may differently affect the calculation of S_I from the iv *vs.* the oral test requires further examination.

Another possible explanation for the finding of $S_{I(oral)} > S_{I(FSIGT)}$ is related to the different routes of glucose and insulin appearance during the meal and the FSIGT. During the meal, both glucose and insulin reach the peripheral circulation after passing through the portal vein. In contrast, during the insulin-modified FSIGT, glucose is injected iv, and the insulin concentration is the result of a mix of endogenously secreted insulin and exogenously administered insulin, the latter component being predominant after insulin injection at 20 min. The possibility that $S_{I(FSIGT)}$ is influenced by the use of peripheral, rather than portal, insulin delivery appears unlikely in view of the recent evidence from Steil *et al.* (21). These investigators demonstrated directly, by portal *vs.* peripheral infusion, that during the FSIGT portal insulin delivery *per se* does not significantly affect insulin's ability to inhibit hepatic glucose release after an iv glucose challenge. Thus, it does not seem likely that in the present study $S_{I(FSIGT)}$ was underestimated with respect to $S_{I(oral)}$ due to the use of peripherally administered exogenous insulin during the FSIGT. A far as the different route of glucose administration is concerned, Cherrington and co-workers (22) have reported evidence suggesting that when glucose enters the systemic circulation through the portal vein, a neurally mediated portal signal is triggered that enhances glucose uptake by the liver. However, as this portal signal appears to inhibit nonhepatic glucose uptake by an amount identical to the amount it increases hepatic glucose uptake, the insulin sensitivity of glucose-consuming tissues should not be affected. Whether such a portal signal is also able to enhance the inhibitory effect of insulin on hepatic glucose production (which would augment the overall insulin sensitivity) is still unknown.

Another factor that could contribute to augment $S_{I(oral)}$ with respect to $S_{I(FSIGT)}$ is GLP-1. Specifically, while GLP-1 is a known insulin secretagogue, there is some evidence that this peptide may stimulate insulin-independent glucose disposal in peripheral tissues (23). Alternatively, there may be other gastrointestinal factors enhancing insulin sensitivity at the liver or muscle that remain to be identified.

Another factor that may play some role is glucagon. It is worth emphasizing that the effects of glucagon on glucose metabolism are not explicitly described by the minimal model. In fact, the model interprets glucose and insulin data, during both the meal and the FSIGT, as the result of the effects of only two factors: glucose effectiveness and insulin sensitivity. Thus, it is possible that the different patterns of glucagon secretion during the FSIGT and the meal may alter the calculation of S_I. The glucagon concentration is inhibited in either the FSIGT or meal protocol. There are, however, contrasts in the patterns by which glucagon returns to its basal level. During a meal, glucagon begins a slow resumption to the basal level after approximately 90 min (24). In contrast, during the insulin-modified FSIGT, glucagon shows a rapid and marked increase after 30 min that counteracts the glucose-lowering effect achieved by means of the exogenous insulin injection (21). An increasing glucagon has two concomitant and

opposite effects on hepatic glucose production: it stimulates hepatic glucose production and potentiates insulin inhibitory effect on hepatic glucose production. The net effect observed by Steil *et al.* was a quick resumption of hepatic glucose production from nearly complete suppression back to basal [in humans, as shown by Vicini *et al.* (25), hepatic glucose production also exhibits a marked overshoot over the baseline]. It can be speculated that this behavior of hepatic glucose production, occurring in concomitance with a still elevated insulin profile, is likely to be interpreted by the minimal model as the inability of insulin to maintain the inhibition of hepatic glucose production. This might lead to an underestimation of insulin sensitivity during the insulin-modified FSIGT, and thus contribute to reduce $S_{I(FSIGT)}$ with respect to $S_{I(oral)}$.

Glucose uptake is dependent upon insulin-independent as well as insulin-dependent mechanisms. In the present oral-based method the insulin-independent component, glucose effectiveness, was assumed. Fortunately, however, the resulting insulin sensitivity value was virtually independent of the estimate of glucose effectiveness. A ±50% change in glucose effectiveness produces only a ±2.3% change in the estimate of $S_{I(oral)}$. Thus, at least in normal subjects, the MGTT/OGTT estimate of S_I does not seem to depend on the assumed value for glucose effectiveness. However, the relative importance of glucose effectiveness to overall glucose tolerance increases substantially in subjects with impaired glucose tolerance as well as those with type 2 diabetes. Thus, the relative unimportance of the estimate of effectiveness to the insulin sensitivity value requires additional examination in different groups of volunteers.

Clearly, calculating insulin sensitivity from an oral test is appealing. Insulin sensitivity derived from MGTT/OGTT data appears to require only eight glucose/insulin samples between 0 and 180 min. In fact, the mean value of $S_{I(oral)}$ and its degree of correlation with $S_{I(FSIGT)}$ did not change when only eight samples (two basal samples and one sample every 30 min until 180 min) were used in AUC calculations.

In conclusion, a new approach for the estimation of insulin sensitivity from a meal tolerance test has been presented that exploits the minimal model approach. The S_I index obtained with this approach in normal subjects appears to be closely associated to the one estimated from insulin-modified FSIGT data. Therefore, our results indicate that the minimal model applied to the analysis of MGTT/OGTT data is potentially useful to measure insulin sensitivity when use of the insulin-modified FSIGT is not feasible for economic or practical reasons. The present study in normal humans is the first attempt and an obvious prerequisite. Further work is needed to define the domain of validity of this method throughout the whole range of insulin sensitivity and assess its applicability to patients with diabetes mellitus. If validated in disease states, the new test may be preferable to the FSIGT in large studies because of its simplicity.

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Appendix

The purpose here is to show how insulin sensitivity can be calculated from MGTT/OGTT data. Making reference to Fig. 1, we denote with $Ra_{ABS}(t)$ ($mgkg^{-1}min^{-1}$) the rate of appearance of the ingested glucose into the systemic circulation during a MGTT/OGTT. To give $Ra_{ABS}(t)$ a parsimonious representation, we make the assumption that its profile resembles an anticipated version of the glucose excursion above basal, $\Delta g(t)=g(t)-g_b$. The simplest functional relationship between Ra_{ABS} and Δg accounting for this idea is the following:

$$\Delta\dot{g}(t) = -a\Delta g(t) + bRa_{ABS}(t) \tag{A1}$$

where a is a parameter governing the degree of delay and smoothness of Δg with respect to Ra_{ABS} and b is a scale factor. Ra_{ABS} can thus be written as follows:

$$Ra_{ABS}(t) = \frac{[a\Delta g(t) + \Delta\dot{g}(t)]}{b} \tag{AII}$$

For the sake of simplicity, we assume that Δg is always nonnegative during the test. We will deal after with the more general case in which glucose concentration displays an undershoot below its basal level in the final part of the test.

Substituting the expression for $Ra_{ABS}(t)$ given by Eq AII into the minimal model equations yield:

$$\dot{g}(t) = -[p_1 + x(t)]g(t) + p_1g_b + \frac{[a\Delta g(t) + \Delta\dot{g}(t)]}{bV}; \quad g(0) = g_b \tag{AIII}$$

$$\dot{x}(t) = -p_2x(t) + p_3[i(t) - i_b]; \qquad x(0) = 0$$

Integrating the equation describing insulin action dynamics (second differential equation in Eq AIII), one obtains the following expression for $S_{I(oral)}$:

$$S_{I(oral)} = \frac{p_3}{p_2}V = \frac{\int_0^\infty x(t)dt}{\int_0^\infty [i(t) - i_b]dt}V \tag{AIV}$$

The integral at the denominator is simply the area under the curve of the measured incremental insulin concentration; the integral at the numerator can be evaluated by integrating the equation describing glucose dynamics (first differential equation in Eq. AII):

$$\int_0^\infty x(t)dt = \left(\frac{a}{bV} - p_1\right)\int_0^\infty \frac{\Delta g(t)}{g(t)}dt + \left(\frac{1}{bV} - 1\right)\int_0^\infty \frac{\Delta\dot{g}(t)}{g(t)}dt \tag{AV}$$

It is easy to show that the second integral in the right member of Eq AV is zero. In fact, assuming that the end of the perturbation the glucose system returns at the pretest steady state we have:

$$\int_0^\infty \frac{\Delta\dot{g}(t)}{g(t)}dt = \int_0^\infty \frac{\dot{g}(t)}{g(t)}dt = \int_0^\infty \frac{d}{dt}[\ln g(t)]dt = \ln g(\infty) - \ln g(0) = 0 \tag{AVI}$$

Substituting Eq AV for Eq AIV and taking into account the result of Eq AVI we obtain:

$$S_{I(oral)} = \frac{\left(\frac{a}{b} - p_1 V\right)\int_0^{\infty}\frac{\Delta g(t)}{g(t)}dt}{\int_0^{\infty}\Delta i(t)dt} \qquad \text{(AVII)}$$

where p_1 V measures glucose effectiveness ($dlkg^{-1}\,min^{-1}$). The ratio a/b is proportional to the amount of glucose that is absorbed during the test. In fact, by integrating Eq All from 0 to infinity we have:

$$\frac{a}{b} = \frac{\int_0^{\infty} Ra_{ABS}(t)dt}{\int_0^{\infty}\Delta g(t)dt} = \frac{f \cdot D_{oral}}{\int_0^{\infty}\Delta g(t)dt} \qquad \text{(AVIII)}$$

where the intergal of Ra_{ABS} is the amount of glucose that has been absorbed. This amount can be conveniently expressed as a fraction, f, of the amount of glucose that has been ingested, D_{oral}. By substituting Eq AVIII into Eq AVII, using the position GE = p_1 V, and denoting, for the sake of simplicity, the intergal from 0 to infinity with the symbol AUC (area under the curve), we have the following expression for insulin sensitivity:

$$S_{I(oral)} = \frac{f \cdot D_{oral}\dfrac{AUC[\Delta g(t)/g(t)]}{\mathrm{AUC}[\Delta g(t)]} - GE \cdot AUC[\Delta g(t)/g(t)]}{\mathrm{AUC}[\Delta i(t)]} \qquad \text{(AIX)}$$

Let us now consider the more general case in which glucose exhibits an excursion below the pretest basal level and let us denote with t_0 the time when glucose concentration crosses the baseline level and begins its undershoot (note that t_0 can be evaluated in each individual by linearly interpolating the glucose samples that immediately precede and follow the crossing of the baseline glucose level). In this case, the use of Eq AII to describe Ra_{ABS} throughout the experiment would imply that Ra_{ABS} becomes negative from some time before t_0 (Ra_{ABS} is an anticipated version of Δg) until the end of the experiment. To cope with such inadequacy of Eq AII (but retaining at the same time the simplicity and usefulness of its description of Ra_{ABS}) we split the description of Ra_{ABS} by distinguishing the intervals that precede and follow t_0:

$$Ra_{ABS}(t) = \begin{cases} \dfrac{[a\Delta g(t) + \Delta \dot{g}(t)]}{b} & for\ t < t_0 \\ -\dfrac{[a\Delta g(t) + \Delta \dot{g}(t)]}{b} & for\ t \geq t_0 \end{cases} \qquad \text{(AX)}$$

According to Eq AX, Ra_{ABS} has an abrupt change of sign in t_0. In this way we limit to a minimum the interval where Ra_{ABS} becomes negative and keeps on using a parametric description of Ra_{ABS} that allows derivation of a simple formula for insulin sensitivity. In fact, using the same rationale outlined above we obtain the following expression for $S_{(oral)}$:

$$S_{I(oral)} = \frac{f \cdot D_{oral}\dfrac{AUC[\Delta g(t)/g(t)]_0^{t_0} - AUC[\Delta g(t)/g(t)]_{t_0}^{\infty}}{AUC[\Delta g(t)]_0^{t_0} - AUC[\Delta g(t)]_{t_0}^{\infty}} - GE \cdot AUC[\Delta g(t)/g(t)]}{\mathrm{AUC}[\Delta i(t)]} \qquad \text{(AXI)}$$

The only diffrence with respect Eq AIX lies in the fraction multiplying $f \cdot D_{oral}$: the AUCs of Ag/g and Δg are separately calculated in the intervals 0-t_0 and to- and the negative AUC calculated in the interval t_0-∞ is subtracted from the positive AUC calculated in the interval 0-t_0.

References

1. **Reaven GM.** 1988 Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 37:1595–1607.
2. **Howard G, O'Leary DH, Zaccaro D, et al.** 1996 Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation. 93:1809–1817.
3. **Kim YI.** 1998 Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? Nutr Rev. 56:275–279.
4. **Bergman RN, Finegood DT, Ader M.** 1985 Assessment of insulin sensitivity *in vivo*. Endocr Rev. 6:45–86.
5. **Kahn SE, Prigeon RL, McCulloch DK, et al.** 1993 Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Evidence for a hyperbolic function. Diabetes. 42:1663–1672.
6. **Bergman RN, Ider YZ, Bowden CR, Cobelli C.** 1979 Quantitative estimation of insulin sensitivity. Am J Physiol. 236:E667–E677.
7. **Saad MF, Anderson RL, Laws A, et al.** 1994 A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Insulin Resistance Atherosclerosis Study. Diabetes. 43:1114–1121.
8. **Owens DR, Luzio SD, Coates PA.** 1996 Insulin secretion and sensitivity in newly diagnosed NIDDM Caucasians in the UK. Diabet Med. 13:S19–S24.
9. **Cobelli C, Vicini P, Toffolo G, Caumo A.** 1997 The hot IVGTT minimal models: simultaneous assessment of disposal indices and hepatic glucose release. In: Lovejoy J, Bergman RN, eds. The minimal model approach and determinants of glucose tolerance. Baton Rouge: Louisiana State University Press; vol 262:E968–E975.
10. **Bergman RN, Prager R, Volund A, Olefsky JM.** 1987 Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest. 79:790–800.
11. **Caumo A, Vicini P, Cobelli C.** 1996 Is the minimal model too minimal? Diabetologia. 39:997–1000.
12. **Caumo A, Vicini P, Zachwieja JJ, et al.** 1999 Undermodeling affects minimal model indexes: insights from a two-compartment model. Am J Physiol. 276:E1171–E1193.
13. **Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN.** 1996 Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care. 19:1018–1030.
14. **Livesey G, Wilson PD, Dainty JR, et al.** 1998 Simultaneous time-varying systemic appearance of oral and hepatic glucose in adults monitored with stable isotopes. Am J Physiol. 275:E717–E728.
15. **Taylor R, Magnusson I, Rothman DL, et al.** 1997 Direct assessment of liver glycogen storage by ^{13}C nuclear magnetic resonance spectroscopy and regulation of glucose homeostasis after a mixed meal in normal subjects. J Clin Invest. 97:126–132.
16. **Wagenknecht LE, Mayer EJ, Rewers M, et al.** 1995 The insulin resistance atherosclerosis study (IRAS) objectives, design, and recruitment results. Ann Epidemiol. 5:464–472.
17. **Valle T, Tuomilehto J, Bergman RN, et al.** 1998 Mapping genes for NIDDM. Design of the Finland-United States Investigation of NIDDM Genetics (FUSION) Study. Diabetes Care. 21:949–958.
18. **Pacini G, Bergman RN.** 1986 MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed. 23:113–122.
19. **Mari A.** 1997 Assessment of insulin sensitivity with minimal model: role of model assumptions. Am J Physiol. 272:E925–E934.
20. **Bettini F, Caumo A, Cobelli C.** Minimal models in the meal-like protocols: simulation studies to assess precision and physiological plausibility of parameter estimates. Proc of the 17th Annual Int Conf of the IEEE-EMBS. 1995; 1361–1362.
21. **Steil GM, Rebrin K, Mittelman SD, Bergman RN.** 1998 Role of portal insulin delivery in the disappearance of intravenous glucose and assessment of insulin sensitivity. Diabetes. 47:714–720.
22. **Cherrington AD.** 1999 Banting Lecture 1997. Control of glucose uptake and release by the liver in vivo. Diabetes. 48:1198–1214.
23. **Kieffer TJ, Habener JF.** 1999 The glucagon-like peptides. Endocr Rev. 20: 876–913.
24. **Butler PC, Rizza RA.** 1991 Contribution to postprandial hyperglycemia and effect on initial splanchnic glucose clearance of hepatic glucose cycling in glucose-intolerant or NIDDM patients. Diabetes. 40:73–81.
25. **Vicini P, Zachwieja JJ, Yarasheski KE, Bier DM, Caumo A, Cobelli C.** 1999 Glucose production during an IVGTT by deconvolution: validation with the tracer-to-tracee clamp technique. Am J Physiol. 276:E285–E294.