Insulin sensitivity by oral glucose minimal models: validation against clamp

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Submitted 22 February 2005; accepted in final form 10 July 2005

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Measuring insulin sensitivity in the presence of physiological changes in glucose and insulin concentrations, e.g., during a meal or OGTT, is important to better understand insulin resistance in a variety of metabolic conditions. Recently, two oral minimal models have been proposed to measure overall insulin sensitivity (Si) and its selective effect on glucose disposal (Si') from oral tests. Si and Si' have been successfully validated against multiple-tracer meal estimates, but validation against euglycemic hyperinsulinemic clamp estimates is lacking. Here, we do so in 21 subjects who underwent both a multiple-tracer OGTT and a labeled euglycemic hyperinsulinemic clamp. Correlation between minimal-model Si, Si' and corresponding clamp estimates Si*clamp, Si'*clamp was satisfactory, respectively r = 0.81, P < 0.001, and r = 0.71, P < 0.001. Si was significantly lower than Si*clamp (8.08 ± 0.89 vs. 13.66 ± 1.69 10-4 dl·kg-1·min-1 per μU/ml, P = 0.0002), whereas Si' and Si'*clamp were very similar (8.17 ± 1.59 vs. 8.84 ± 1.39 10-4 dl·kg-1·min-1 per μU/ml, P = 0.52). These results add credibility to the oral minimal-model method as a simple and reliable physiological tool to estimate Si and Si', also in large-scale clinical trials.

Methods

Subjects and Protocol

Twenty-one subjects (8 females, 13 males) with varying degrees of glucose tolerance [10 normal glucose tolerance (NGT) and 11 impaired glucose tolerance (IGT); age = 41 ± 1 yr; BMI = 27 ± 1 kg/m2 in NGT and 34 ± 2 kg/m2 in IGT; body surface area (BSA) = 1.89 ± 0.06 in NGT and 2.01 ± 0.06 in IGT] underwent both a labeled euglycemic hyperinsulinemic clamp and an OGTT labeled with two glucose tracers. Experimental procedures were reviewed and approved by the Institutional Review Board at Washington University School of Medicine. All subjects provided informed consent.

Euglycemic Hyperinsulinemic Clamp

The labeled euglycemic hyperinsulinemic clamp consisted of a tracer equilibration period (from t = 0 to 120 min) and a glucose clamp period (from t = 120 to 300 min). During the tracer equilibration period, a primed continuous infusion of [2H2]glucose (Cambridge Isotope Laboratories, Andover, MA) was administered, with the priming dose

\[
\text{BSA} = \begin{cases} 
180 \text{ mg} \cdot \text{m}^{-2} \cdot \text{min}^{-1} & \text{lean} \\
180 \text{ mg} \cdot \text{m}^{-2} \cdot \text{min}^{-1} & \text{obese} \\
90 \text{ mg} \cdot \text{m}^{-2} \cdot \text{min}^{-1} & \text{continuous infusion} \\
\text{BSA} & \text{BSA}
\end{cases}
\]

where BSA is body surface area (m²). Plasma samples were collected at -5, 0, 2, 3, 5, 7, 10, 15, 20, 25, 30, 40, 50, 75, 90, 100, 110, and 120 min. Regular human insulin (Novo Nordisk, Princeton, NJ) was infused to maintain glucose concentration at its basal level in each individual; the infusion was adjusted according to the arterialized glucose concentration determined every 5 min.

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Plasma samples were collected at 130, 140, 150, 170, 190, 210, 230, 240, 250, 260, 270, 280, 290, and 300 min.

**Labeled OGTT**

OGTT consisted of oral administration of 75 g of glucose at time 0 (71 g unlabeled glucose, 4 g [U-13C6]glucose tracer); glucose tracer concentration (G*) was used to derive the exogenous, i.e., coming from the oral load, glucose concentration (Gogtt) as:

\[ G_{ogtt} = G^* \cdot \left( 1 + \frac{1}{z_{ogtt}} \right) \]  

(2)

where \( z_{ogtt} \) is the tracer-to-tracee ratio in the OGTT. A variable intravenous infusion of [\( ^{2} \text{H}_{2} \text{H} \)] glucose was given with the tracer-to-tracee clamp technique, i.e., mimicking the expected profile of the Rg of ingested glucose. Pump rate was 5–10 min at 0.1 ml/min; 10–50 min at 0.46 ml/min; 50–90 min at 0.29 ml/min; 90–150 min at 0.19 ml/min; 150–180 min at 0.11 ml/min; 180–210 min at 0.044 ml/min; 210–300 min at 0.01 ml/min; and 300–360 min at 0.005 ml/min.

It is of note that, in Ref. 2, three tracers were administered [one given with the meal: [1-13C]glucose; two given intravenously: [6,6-\( ^{2} \text{H}_{2} \text{H} \)] glucose mimicking endogenous glucose production (EGP) and [\(^{2} \text{H}_{2} \text{H} \)] glucose mimicking Rg] to assess not only the Rg of orally administered glucose, but also EGP. In the present paper, only two tracers were used (oral, [U-13C6]glucose; iv, [6,6-\( ^{2} \text{H}_{2} \text{H} \)] glucose), because the purpose here is to derive a model-independent estimate of Rg.

Blood samples were collected at -15, 0, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180, 210, 240, 270, 300, and 360 min. Capillary gas chromatography-quadruple mass-spectrometry was used to quantitate [6,6-\( ^{2} \text{H}_{2} \text{H} \)]- and [U-13C6]glucose enrichments (6, 19, 23). Plasma samples (200 μl) were deproteinized with cold acetonitrile (200 μl), and the pentacetate derivative of glucose was formed. The derivatized sample was analyzed on an Agilent 5970 Mass Selective Detector (Palo Alto, CA) with positive chemical ionization capabilities and fitted with a DB-1 capillary column. Selected ion monitoring was used to quantify the signal intensities for the ions at mass-to-charge ratios (m/z) 331, 333, and 337. The tracer-to-tracee ratios ([6,6-\( ^{2} \text{H}_{2} \text{H} \)]- and [U-13C6]glucose enrichments) were calculated as described in Refs. 25 and 26.

**Insulin Sensitivity from Clamp**

Insulin sensitivity. Insulin sensitivity (\( S_{\text{clamp}}^{t} \)) was calculated from plasma glucose and insulin concentrations and glucose rate of infusion as (3, 17):

\[ S_{\text{clamp}}^{t} = \frac{\text{GIR}_{\text{m}}}{\text{G}_{\text{m}} \cdot \Delta t} \]  

(3)

where \( \text{GIR}_{\text{m}} \) (mg·kg\(^{-1}\)·min\(^{-1}\)) is the steady-state (average in the last 40 min) glucose infusion rate, \( \text{G}_{\text{m}} \) is the steady-state glucose concentration, and \( \Delta t \) is the difference between end-test and basal insulin concentration.

Insulin sensitivity on glucose disposal. Insulin sensitivity on glucose disposal was calculated from [\( ^{2} \text{H}_{2} \text{H} \)] glucose and insulin plasma concentrations and from tracer GIR as (3):

\[ S_{\text{clamp}}^{\text{g}} = \frac{\Delta \text{GIR}_{\text{g}}}{z_{\text{ogtt}} \cdot \text{G}_{\text{g}} \cdot \Delta t} \]  

(4)

where \( \Delta \text{GIR}_{\text{g}} \) (mg·kg\(^{-1}\)·min\(^{-1}\)) is the difference between steady-state (average in the last 40 min) tracer infusion rate at the end of the clamp period and during the tracer equilibration period; \( z_{\text{ogtt}} \) is the end-test tracer-to-tracee ratio, i.e., [\( ^{2} \text{H}_{2} \text{H} \)] glucose/glucone; \( \text{G}_{\text{g}} \) is the steady-state glucose concentration; and \( \Delta t \) is the difference between end-test and basal insulin concentration.

**Insulin Sensitivity from Oral Minimal Models**

Oral minimal model. The oral minimal model (OMM) (14, 15) uses the changes in plasma glucose and insulin concentrations observed after the OGTT glucose dose to derive \( S_{\text{I}} \) and the \( R_{\text{a,ogtt}} \). Model equations are (4):

\[ \begin{align*}
G(t) &= -[S_{t} + X(t)] \cdot G_{1} + S_{t} \cdot G_{0} + \frac{R_{a,ogtt}(\alpha)}{V} \\
X(t) &= -p_{2} \cdot X(t) + p_{3} \cdot [I(t) - I_{b}] \\
X(0) &= 0
\end{align*} \]  

(5)

where \( G \) is plasma glucose concentration, \( I \) is plasma insulin concentration, suffix “b” denotes basal values, \( X \) is insulin action on glucose production and disposal, \( V \) is distribution volume, and \( S_{t}, p_{2}, \) and \( p_{3} \) are model parameters. Specifically, \( S_{t} \) is the fractional (i.e., per unit distribution volume) glucose effectiveness, which measures glucose ability per se to promote glucose disposal and inhibit glucose production; \( p_{2} \) is the rate constant describing the dynamics of insulin action; \( p_{3} \) is the parameter governing the magnitude of insulin action. \( R_{a,ogtt} \) is described as a piecewise-linear function with known break points \( t_{i} \) (5, 15, 30, 60, 90, 120, 240, 360 min) and unknown amplitude \( \alpha_{i} \):

\[ R_{a,ogtt}(\alpha_{i}) = \left\{ \begin{array}{ll}
\alpha_{i-1} + \frac{\alpha_{i} - \alpha_{i-1}}{t_{i} - t_{i-1}} & \text{for } t_{i-1} \leq t \leq t_{i}, \quad i = 1 \ldots 7 \\
0, \text{Otherwise}
\end{array} \right. \]  

(6)

with \( \alpha \) denoting \( (\alpha_{1}, \alpha_{2}, \ldots, \alpha_{7})^{T} \).

Insulin sensitivity is given by (14, 15):

\[ S_{I} = \frac{P_{3}}{P_{2}} \cdot V \text{ (dl · kg}^{-1} \text{·min}^{-1} \text{per μU/ml)} \]  

(7)

Labeled OMM. The labeled OMM, OMM*, uses exogenous glucose \( G_{ogtt} \), to derive \( S_{I}^{*} \) (effect of insulin on glucose disposal) and \( R_{a,ogtt} \) (13); it is described by

\[ \begin{align*}
G(t) &= -[S_{t}^{*} + X^{*}(t)] \cdot G_{1} + S_{t}^{*} \cdot G_{0} + \frac{R_{a,ogtt}(\alpha_{t})}{V^{*}} \\
X^{*}(t) &= -p_{2}^{*} \cdot X^{*}(t) + p_{3}^{*} \cdot [I(t) - I_{b}] \\
X^{*}(0) &= 0
\end{align*} \]  

(8)

where \( G_{ogtt} \) is exogenous glucose concentration, \( I \) is plasma insulin concentration, \( X^{*} \) is insulin action on glucose disposal, \( V^{*} \) is distribution volume, and \( S_{t}^{*}, p_{2}^{*}, \) and \( p_{3}^{*} \) are model parameters. Specifically, \( S_{t}^{*} \) is the fractional (i.e., per unit distribution volume) glucose effectiveness, which measures glucose ability per se to promote glucose disposal; \( p_{2}^{*} \) is the rate constant describing the dynamics of insulin action on glucose disposal, and \( p_{3}^{*} \) is the parameter governing its magnitude. Insulin sensitivity on glucose disposal is calculated as (13)

\[ S_{I}^{*} = \frac{P_{3}^{*}}{P_{2}^{*}} \cdot V^{*} \text{ (dl · kg}^{-1} \text{·min}^{-1} \text{per μU/ml)} \]  

(9)

**Reference Model and Reference Model***

Both OMM and OMM* contain a parametric description of \( R_{a,ogtt} \), the parameters of which must be estimated from the data. An additional model-independent estimate of glucose Rf during OGTT was derived for each subject (\( R_{a,ogtt}^\text{def} \)), by applying the Steele equation to the clamped tracer-to-tracee ratio \( TTR = \frac{[^{2} \text{H}_{2} \text{H}]}{\text{HO2} \text{H} \text{O}} \), as explained in detail in Ref. 2:

\[ R_{s,ogtt}(t) = \frac{F(t)}{TTR(t)} - p \cdot V \cdot G_{ogtt}(t) \cdot \frac{d\text{TTR}(t)}{dt} \]  

(10)

where \( F(t) \) is the pump infusion profile of [\( ^{2} \text{H}_{2} \text{H} \)] glucose, \( V \) is the distribution volume of glucose, \( p \) is the pool fraction, and \( G_{ogtt} \) is
defined by Eq. 2. Taking into account the derivative of TTR in Eq. 10 minimizes the non-steady-state error that occurs if the intravenous tracer is infused with a profile different from the $R_a$ to be estimated. In fact, with the tracer-to-tracee clamp method, one needs to know $R_a$ to correctly infuse the tracer and maintain TTR constant; however, this not possible in practice because $R_a$ is unknown (9).

$R_{a\,\text{opt}}^{\text{ref}}$ was used to validate the estimated $R_a^{\text{opt}}$ and as known input of Reference Model (RM) and labeled Reference Model (RM*):

$$
\left\{ \begin{array}{l}
G(t) = - \left[ S_I^{\text{ref}} + X(t) \right] \cdot G(t) + S_{I_0}^{\text{ref}} \cdot G_b + \frac{R_{a\,\text{opt}}^{\text{ref}}(t)}{V_{\text{ref}}} \cdot G(0) = G_b \\
X(t) = - p_{I_1}^{\text{ref}} \cdot X(t) + p_{S_1}^{\text{ref}} \cdot \left[ I(t) - I_b \right] \\
\end{array} \right.
$$

$$
X(0) = 0
$$

Identification

Identifiability. OMM and OMM* were simultaneously identified on $G$ and $G_{opt}$ data; since $V$ and $V^*$ are not identifiable and $S_G$ and $S_{S_0}$ are not uniquely identifiable (see Ref. 15 for details), $V$, $V^*$ and $S_G$, $S_{S_0}$ were fixed to the mean values obtained with RM and RM*, i.e., $V = V_{\text{ref}}, V^* = V_{\text{ref}}^{\text{ref}}, S_G = S_G^{\text{ref}}$, $S_{S_0} = S_{S_0}^{\text{ref}}$, whereas parameters $p_2$, $p_3$, $p_4$, $p_5$, and $\alpha_1 \ldots \alpha_5$ were estimated in each individual. As in Refs. 14 and 15, the area under $R_a^{\text{opt}}$ was constrained to equal the total amount of ingested glucose, $D$ multiplied by the fraction that is actually absorbed, $f$ (fixed to the mean value obtained from the $R_{a\,\text{opt}}^{\text{ref}}$ profiles, $f = 0.87$). Moreover, the availability of oral tracer measurements provided information about when $R_a^{\text{opt}}$ began to rise in each subject: if tracer concentration is zero up to time $t_1$ and is different from zero at time $t_1 + 1$, then one can safely assume that $R_a^{\text{opt}}$ is zero up to $t_1$.

Parameter estimation. All models were numerically identified by nonlinear least squares (8, 11) as implemented in SAAM II [Simulation Analysis and Modeling software (1)]. Measurement error on glucose and [U-13C6]glucose data were assumed to be independent, Gaussian, with zero mean and constant fractional standard deviation (CV = 2 and 6%, respectively).

Statistical Analysis

Data are presented as means ± SE. Two sample comparisons were done by Wilcoxon signed rank test (significance level set to 5%). Pearson’s correlation was used to evaluate univariate correlation.

RESULTS

Plasma Concentrations

Figure 1 shows the clamp mean glucose, tracer glucose, and insulin plasma concentrations. Figure 2 shows the OGTT mean glucose, exogenous glucose, and insulin plasma concentrations. The clamped TTR = [2H2]glucose/$G_{\text{opt}}$, obtained during the OGTT, is shown in Fig. 3. It is worth noting that TTR doubles during the experiment; however, most of the variation is in the last 180 min, where the $R_a$ is approximately zero; thus this nonconstancy will modestly affect the estimated profile. However, to minimize the nonconstancy effect of TTR (the non-steady-state error), a non-steady-state correction was employed (Eq. 10) by taking into account the derivative of TTR.

\[ \text{Net clamp insulin sensitivity} = \frac{S_{I_1}^{\text{clamp}}}{S_{I_1}} = 13.66 \pm 1.69 \text{ min}^{-1} \cdot \text{dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per } \mu\text{U/ml} \]

\[ \text{Net clamp oral insulin sensitivity} = \frac{S_{I_1}^{\text{clamp}}}{S_{I_1}} = 8.84 \pm 1.39 \times 10^{-4} \text{ dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per } \mu\text{U/ml} \]

Reference parameters estimated with RM and RM* are:

- $S_G = 0.028 \pm 0.003 \text{ min}^{-1}$ (CV = 15 ± 2%); $V_{\text{ref}} = 1.34 \pm 0.06 \text{ dl/kg}$ (CV = 5 ± 0.3%); $p_{2\,\text{ref}} = 0.0123 \pm 0.0023 \text{ min}^{-1}$ (CV = 19 ± 3%); $S_{I_1}^{\text{ref}} = 8.18 \pm 0.96 \text{ dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per } \mu\text{U/ml}$ (CV = 11 ± 2%); $S_{G_2}^{\text{ref}} = 0.0067 \pm 0.006 \text{ min}^{-1}$ (CV = 15 ± 3%) $V_{\text{ref}} = 1.48 \pm 0.07 \text{ dl/kg}$ (CV = 4 ± 0.1%); $p_{2\,\text{ref}} = 0.042 \pm 0.004 \text{ min}^{-1}$ (CV = 14 ± 1%); and $S_{G_2}^{\text{ref}} = 8.00 \pm 1.19 \text{ dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per } \mu\text{U/ml}$ (CV = 8 ± 1%).

$S_{I_1}$, $S_{I_1}^{\text{ref}}$, and $R_{a\,\text{opt}}^{\text{ref}}$

Oral minimal models $S_{I_1}$, $S_{I_1}^{\text{ref}}$ are estimated with good precisions. Mean values are $S_{I_1} = 8.08 \pm 0.89$ (CV = 6 ± 1%) and $S_{I_1}^{\text{ref}} = 8.17 \pm 1.59 \times 10^{-4} \text{ dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per } \mu\text{U/ml}$ (CV = 3 ± 1%). The model-reconstructed $R_{a\,\text{opt}}^{\text{ref}}$ (Fig. 4) is in good agreement with the model-independent $R_{a\,\text{opt}}^{\text{ref}}$ obtained using the tracer-to-tracee clamp technique. $S_{I_1}$ and $S_{I_1}^{\text{ref}}$ were virtually identical to, respectively, $S_{I_1}^{\text{ref}}$ and $S_{I_1}^{\text{ref}}$, obtained using $R_{a\,\text{opt}}^{\text{ref}}$ as a
known input: 8.08 ± 0.89 vs. 8.18 ± 0.96 (P = 0.72) and 8.17 ± 1.59 vs. 8.00 ± 1.19 (P = 0.79).

$S_I$ vs. $S_I^{\text{clamp}}$ and $S^{\#}_I$ vs. $S^{\#}_I^{\text{clamp}}$

Oral models and clamp measurements of insulin sensitivity were well correlated (Fig. 5): $r = 0.81$, $P < 0.001$ for $S_I$ vs. $S_I^{\text{clamp}}$ and $r = 0.70$, $P < 0.001$ for $S_I^{\#}$ vs. $S^{\#}_I^{\text{clamp}}$. $S_I$ was lower than $S_I^{\text{clamp}}$ by 34%: 8.08 vs. 13.66 $10^{-4}$ dl·kg$^{-1}$·min$^{-1}$ per µU/ml ($P = 0.0002$), whereas $S^{\#}_I$ was similar to $S^{\#}_I^{\text{clamp}}$: 8.17 vs. 8.84 $10^{-4}$ dl·kg$^{-1}$·min$^{-1}$ per µU/ml ($P = 0.52$).

DISCUSSION

The oral, OMM, and the labeled oral, OMM*, glucose minimal models provide reliable measurements of the overall effect of insulin to stimulate glucose disposal and inhibit glucose production, $S_I$, as well as of the effect to stimulate glucose utilization and production increases linearly with insulin concentration across the insulin range experienced during OGTT and clamp; and insulin sensitivity is independent from the route of insulin delivery, i.e., portal vs. peripheral. As regards the first condition, the OGTT dynamic milieu is well described by single-

Our purpose here was to extend their validity by comparing $S_I$ and $S^{\#}_I$ obtained during an OGTT with those obtained during a euglycemic hyperinsulinemic clamp procedure. Because OGTT is more widely used than a meal to assess glucose tolerance, our study may also broaden the domain of application of the oral minimal model method.

Oral minimal-model insulin sensitivity indexes $S_I$ and $S^{\#}_I$ are well correlated with their counterparts obtained with the euglycemic hyperinsulinemic clamp technique, $S_I^{\text{clamp}}$ and $S^{\#}_I^{\text{clamp}}$, respectively $r = 0.81$ and $r = 0.70$. However, OMM $S_I$ was significantly lower than $S_I^{\text{clamp}}$, whereas OMM* $S^{\#}_I$ was virtually identical to $S^{\#}_I^{\text{clamp}}$.

The good correlation shown between OMM and clamp $S_I$ is similar to that observed when $S_I$ of the IVGTT minimal model is compared against that of the clamp technique (20). An analogous trend toward underestimating $S_I$ was also present when IVGTT $S_I$ was compared with glucose clamp $S_I$. However, as discussed in detail (21), values/comparison of IVGTT and clamp depend on how the IVGTT and clamp are performed (i.e., standard insulin- or tolbutamide-boosted IVGTT; and low-, medium-, or high-dose hyperinsulinemia during the clamp). Similarly, for OMM $S_I$ and $S_I^{\text{clamp}}$ to be equivalent a number of conditions must be met; the most important are that the minimal-model single-pool description of glucose is adequate; insulin action on the combination of glucose utilization and production increases linearly with insulin concentration across the insulin range experienced during OGTT and clamp; and insulin sensitivity is independent from the route of insulin delivery, i.e., portal vs. peripheral. As regards the first condition, the OGTT dynamic milieu is well described by single-

Fig. 4. OGTT rate of appearance ($R_{a_{ogtt}}$) reconstructed by oral minimal models (OMM) is plotted against the model-independent $R_{a_{ogtt}}^{\text{ref}}$.
compartment glucose kinetics, at variance with IVGTT, so we tend to exclude an undermodeling effect on OGTT $S_I$. As regards the second condition, in the current study plasma insulin levels during the clamp were designed to mimic the mean plasma insulin levels observed during an OGTT (40–50 μU/ml), which are within the linear portion of the insulin vs. glucose disposal curve. In fact, although the steady-state relationship between glucose disposal and insulin concentration is approximately linear in the range of 10–100 μU/ml, the relationship between endogenous glucose production and insulin concentration can be safely assumed linear only up to 40–50 μU/ml. Thus these considerations speak in favor of having met the linear assumption, but one has to keep in mind that the time courses of insulin concentration during an OGTT and a glucose clamp are very different (i.e., constant in the clamp, vs. bell shaped during the OGTT). Finally, in comparing $S_I$ with $S_I^{\text{clamp}}$, one assumes that the peripheral and portal routes of insulin delivery are equally effective in inhibiting endogenous glucose production. To the best of our knowledge, the only study addressing this issue is that of Steil et al. (22). In that study, paired insulin-modified IVGTTs were performed in dogs infused with insulin (portal vs. peripheral) while circulating insulin levels were matched. Parameter estimates of $S_I$ under those two different routes of insulin infusion did not differ significantly. Unfortunately no data are available on the contribution of portal insulin to the assessment of $S_I$ during OGTT or meal. However, one has to consider the very different physiological milieu seen by the liver during clamp and OGTT, i.e., a constant insulin level of 40–50 μU/ml vs. a bell-shaped insulin time course with a maximum of approximately three times the peripheral concentration, i.e., 240 μU/ml (see also below).

The discussion above assumes that OMM parameters accurately describe the manner in which changes in glucose and insulin concentrations regulate endogenous glucose production and disposal rates. We found that insulin action on glucose disposal estimated by OMM* $S_I^*$ was virtually identical to that obtained during the clamp, $S_I^{\text{clamp}}$. This may indicate that the glucose disposal component of OMM is more correctly described than the glucose production component. Thus a possible explanation for the 34% underestimation of OMM $S_I$ (compared with $S_I^{\text{clamp}}$) might be an inadequate description of the control of glucose and insulin on endogenous glucose production by OMM. This potential inaccuracy may also explain the physiologically implausible finding that $S_I$ was greater than $S_I^*$ in 7 of 21 subjects studied here. This paradoxical result has been observed in a large percentage of IVGTT studies (10, 12, 24). In the present OGTT study, the phenomenon has been mitigated, but it is still present in 33% of the subjects.

As in previously reported meal studies (13, 14), the multiple-tracer OGTT was used to reconstruct a model-independent estimate of the appearance rate of ingested glucose, $R_{a\text{ogtt}}^{\text{ref}}$. Thanks to $R_{a\text{ogtt}}^{\text{ref}}$, we have addressed several questions about OMM: is its prediction of $R_a$ reliable? Is there any compensation between $R_a$ and disposal/production model parameters? Figure 4 confirms our previous meal results: OMM reliably predicted the "true" $R_{a\text{ogtt}}$. In addition, when that true input $R_{a\text{ogtt}}^{\text{ref}}$ was used to identify either RM or RM*, identical values of $S_I$ and $S_I^*$ were obtained. This suggests that values for $V$, $S_G$, $f$, and $V^*$, $S_G^*$ for OMM and OMM* identification can be fixed to population averages without introducing appreciable bias in the estimation of $S_I$. However, it is worth noting that when RM* instead of OMM* was used, the correlation between $S_I^*$ and $S_I^{\text{clamp}}$ increased from $r = 0.70$ to 0.83, whereas, if RM instead of OMM is used, correlation between $S_I$ and $S_I^{\text{clamp}}$ does not change ($r = 0.81$ with OMM; $r = 0.80$ with RM). $R_a$ estimate can also be affected by the choice of reference $V$, $S_G$, $V^*$, and $S_G^*$: from a theoretical sensitivity analysis it emerged that the sensitivity of $R_a$ estimate to $V$ and $V^*$ is 1 in each breakpoint $\alpha_i$, thus any error in $V$ or $V^*$ results in a percentage equal error in the calculated $R_a$; luckily, neither $V$ nor $V^*$ varies too much in the population [(Vref − V)/Vref = −4 ± 4%; (Vref − V*)/Vref = −5 ± 6%]. Conversely, the sensitivity of $R_a$ parameters to $S_G$ and $S_G^*$, different in each breakpoint, is lower than 0.64 for $t < 240$ min, whereas it increases until 3.8 in the last part of the experiment; thus, e.g., a 50% error in $S_G$ produces an error <32% in the first 5 $\alpha_i$,
whereas the percentage error can reach 190% for α6 and α7, which, however, are very close to zero.

In conclusion, we have presented good evidence of the ability of OMM and OMM* to assess both the net effect of insulin action on glucose utilization and endogenous production, S1, and the effect of insulin on glucose utilization only, S7, from a labeled OGTT by comparing S1 and S7 with their corresponding gold standard euglycemic hyperinsulinemic clamp values. Future studies should address the physiological explanation for the difference between S1 and S7* values and to assess whether OGTT and meal models of glucose kinetics provide equivalent estimates of insulin action. Despite their limitations, our findings support the reliability of the OMM and OMM* tools for quantifying insulin action in clinical studies using a standardized oral glucose tolerance test. The potential to simultaneously assess β-cell responsivity parameters, advances that will make this

• VOL 289 • DECEMBER 2005 • www.ajpendo.org


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