Measurement of selective effect of insulin on glucose disposal from labeled glucose oral test minimal model

Chiara Dalla Man,1 Andrea Caumo,2 Rita Basu,3 Robert Rizza,3 Gianna Toffolo,1 and Claudio Cobelli1

1Department of Information Engineering, University of Padova, Padua; 2San Raffaele Scientific Institute, Milan, Italy; and 3Division of Endocrinology, Diabetes, Metabolism, and Nutrition Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota

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Dalla Man, Chiara, Andrea Caumo, Rita Basu, Robert Rizza, Gianna Toffolo, and Claudio Cobelli. Measurement of selective effect of insulin on glucose disposal from labeled glucose oral test minimal model. Am J Physiol Endocrinol Metab 289: E909–E914, 2005. First published June 21, 2005; doi:10.1152/ajpendo.00299.2004.—The oral glucose minimal model (OMM) measures insulin sensitivity (S_I) and the glucose rate of appearance (R_a) of ingested glucose in the presence of physiological changes of insulin and glucose concentrations. However, S_I of OMM measures the overall effect of insulin on glucose utilization and glucose production. In this study we show that, by adding a tracer to the oral dose, e.g., of a meal, and by using the labeled version of OMM, OMM* to interpret the data, one can measure the selective effect of insulin on glucose disposal, S^*_I. Eighty-eight individuals underwent both a triple-tracer meal with the tracer-to-tracee clamp technique, providing a model-independent reference of the R_a of ingested glucose (R^*_a) and an insulin-modified labeled intravenous glucose tolerance test (IVGTT*). We show that OMM* provides not only a reliable means of tracing the R_a of ingested glucose (R^*_a) but also accurately measures S^*_I. We do so by comparing OMM* R^*_a with the model-independent R^*_a provided by the tracer-to-tracee clamp technique, while OMM* S^*_I is compared with both S^*_I measured by using as known input R^*_a and with S^*_I measured during IVGTT*.

Insulin action; glucose utilization; tracer-to-tracee activity clamp; intravenous glucose tolerance test; oral glucose tolerance test

The oral minimal model method can simultaneously measure insulin secretion, insulin action, and the rate of glucose appearance after meal or glucose ingestion (3, 6, 11, 12). In particular, the oral glucose minimal model (OMM) measures insulin sensitivity (S_I), as well as the rate of appearance of ingested glucose (R_a of ingested glucose (R^*_a) (11, 12). One limitation of the S_I index measured by OMM is that S_I is a composite index, i.e., it measures the overall effect of insulin to stimulate glucose uptake and inhibit glucose production. At least in theory, the individual contribution of insulin’s ability to stimulate glucose uptake can be measured if a tracer glucose is added to the meal. If so, labeled glucose oral data, analyzed by means of an oral labeled minimal model, can provide an estimate of S_I (S^*_I) reflecting glucose disposal only. This would be reminiscent of the approach that previously led our group to propose the labeled intravenous glucose tolerance test (IVGTT) and its interpretation with the labeled minimal model (10, 14).

The aim of this study is to develop and validate an oral labeled minimal model (OMM*). We show that OMM* provides reliable estimates of disposal S^*_I and R^*_a. To validate OMM*, we took advantage of a unique data set (11) containing 88 individuals who underwent a triple-tracer labeled meal, as well as a labeled IVGTT (IVGTT*). The triple-tracer labeled meal, thanks to the use of the tracer-to-tracee clamp technique, provided a model-independent reference for the appearance rate of ingested glucose (R^*_a) (4). R^*_a was then used as a known input of a model of labeled glucose kinetics. This model, denoted as reference tracer model (RM*), was identified from labeled meal data and yielded a reference measure of disposal insulin sensitivity, S^*_I ref. OMM* is validated by comparing OMM*-based estimates of S^*_I and R^*_a to S^*_I ref and R^*_a ref, respectively. Validation is further strengthened by comparing OMM* S^*_I with the IVGTT* S^*_I measured in the same subjects with the traditional labeled minimal model.

Methods

Data

The database consisted of 88 normal subjects [46 males and 42 females: age = 58 ± 2 yr (range 19–87); body wt = 77 ± 2 kg (range 53–129); BMI = 26.71 ± 0.1 kg/m² (range 20–35); fasting glucose = 92.07 ± 0.7 mg/dl (range 77.29–105.12)] who received both a triple-tracer mixed meal and an IVGTT*

Labeled mixed meal. The triple-tracer mixed meal (10 kcal/kg: 45% carbohydrate, 15% protein, 40% fat) contained 4% of the meal ingested glucose labeled with [6,6-2H2]glucose,

inulin-modified labeled intravenous glucose tolerance test (IVGTT*). We show that OMM* provides not only a reliable means of tracing the R_a of ingested glucose (R^*_a) but also accurately measures S^*_I. We do so by comparing OMM* R^*_a with the model-independent R^*_a provided by the tracer-to-tracee clamp technique, while OMM* S^*_I is compared with both S^*_I ref obtained by using as known input R^*_a and with S^*_I measured during IVGTT*.

OMM*, we took advantage of a unique data set (11) containing 88 individuals who underwent a triple-tracer labeled meal, as well as a labeled IVGTT (IVGTT*). The triple-tracer labeled meal, thanks to the use of the tracer-to-tracee clamp technique, provided a model-independent reference for the appearance rate of ingested glucose (R^*_a) (4). R^*_a was then used as a known input of a model of labeled glucose kinetics. This model, denoted as reference tracer model (RM*), was identified from labeled meal data and yielded a reference measure of disposal insulin sensitivity, S^*_I ref. OMM* is validated by comparing OMM*-based estimates of S^*_I and R^*_a to S^*_I ref and R^*_a ref, respectively. Validation is further strengthened by comparing OMM* S^*_I with the IVGTT* S^*_I measured in the same subjects with the traditional labeled minimal model.

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

where z_{meal} is the tracer-to-tracee ratio in the meal. Plasma samples were collected at –120, –30, –20, –10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, and 420 min.

Figure 1, A–C, left, shows mean glucose, exogenous glucose, and insulin plasma concentration curves. Beginning at time 0, [6,6-H]glucose was infused intravenously at a variable rate, mimicking R_a of [6,6-H]glucose. [6,6-H]glucose was also infused as part of a separate protocol. Because the ratio in plasma between [6,6-H]glucose and [1-13C]glucose was maintained almost constant (Fig. 2A), Steele’s model provided an essentially model-independent estimate of R_a of ingested glucose (R^*_a) (4); total R^*_a was then calculated from R^*_a (Fig. 2B) as

\[ R^*_a = R^*_a \cdot \left[ 1 + \frac{1}{z_{meal}} \right] \]  

Labeled intravenous glucose tolerance test. The IVGTT* consisted of a 330 mg/kg glucose bolus at time 0 labeled with [6,6-2H2]glucose,
followed by a short insulin infusion of 0.02 U/kg between 20 and 25 min. Plasma samples were collected at 1200, 140, 20, 25, 30, 40, 50, 60, 75, 90, 120, 180, and 240 min. Figure 1, A–C, right, shows mean glucose, exogenous glucose, and insulin plasma concentration.

Models

Oral minimal models. For the sake of clarity, a brief description of the “cold” (i.e., unlabeled) oral minimal models (11, 12) precedes the presentation of the new “hot” (i.e., labeled) OMM*. This is done not only because the two oral minimal models hinge on the same monocompartmental structure of glucose kinetics, but also because they share the exogenous glucose input, i.e., Ra meal. Denoting by G the total plasma glucose concentration, the rate of glucose disappearance (Rd) and the net hepatic glucose balance (NHGB) (Fig. 3, left) model equation following Ref. 5 is

\[
\frac{dG}{dt} = -\frac{R_d(t) + NHGB(t) + Ra\text{ meal}(t)}{V}; \quad G(0) = G_0
\]  

where V is the distribution volume.

By assuming for Rd and NHGB the functional description proposed in Ref. 5, one obtains OMM:

\[
\begin{align*}
G(t) &= -[S_0 + X(t)] \cdot G(t) + S_0 \cdot G_0 + \frac{Ra\text{ meal}(\alpha_i)}{V}; \quad G(0) = G_0 \\
X(t) &= -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_0]; \quad X(0) = 0
\end{align*}
\]

where \(S_0\) is fractional (i.e., per unit distribution volume) glucose effectiveness measuring glucose ability per se to promote glucose disposal and inhibit NHGB, I is plasma insulin concentration, X is insulin action on glucose disposal and production, with \(p_2\) and \(p_3\) rate constants describing its dynamics and magnitude; b denotes basal values. \(Ra\text{ meal} \) is described as a piecewise-linear function with known break point \(t_i\) and unknown amplitude \(\alpha_i\):

\[
Ra\text{ meal}(\alpha_i) = \begin{cases} 
\alpha_i - \frac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}}(t - t_{i-1}) & \text{per } t_{i-1} \leq t \leq t_i \quad i = 1 \ldots 8 \\
0 & \text{otherwise}
\end{cases}
\]

with \(\alpha\) denoting \([\alpha_1, \alpha_2, \ldots, \alpha_8]^T\).
Labeled oral minimal model. OMM is unable to distinguish the individual contribution of glucose production and disposal. To overcome this limitation, a glucose tracer is administered orally and unlabeled glucose and plasma concentrations of the glucose tracer are measured. OMM* relies on $G_{\text{meal}}$ (eq. 1), and model equation is

$$G_{\text{meal}}(t) = - \frac{R_{\text{a,meal}}(t) + R_{\text{d,meal}}(t)}{V_{\text{p}}} \quad G_{\text{meal}}(0) = 0$$

where $R_{\text{d,meal}}$ is the $R_d$ of $G_{\text{meal}}$. By assuming for $R_{\text{d,meal}}$ the same functional description proposed previously (10) and for $R_{\text{a,meal}}$ the parametric description of Eq. 5, one obtains OMM* (Fig. 3, middle). Model equations are

$$
\begin{align*}
G_{\text{meal}}(t) &= - \left[ S_G^* + X^*(t) \right] \cdot G_{\text{meal}}(t) + \frac{R_{\text{a,meal}}(\alpha, t)}{V_{\text{p}}} \quad G_{\text{meal}}(0) = 0 \\
X^*(t) &= - p_2^* \cdot X^*(t) + p_1^* \cdot [I(t) - I_0] \quad X^*(0) = 0
\end{align*}
$$

where $S_G^*$ is fractional (per unit distribution volume) glucose effectiveness measuring glucose ability per se to promote glucose disposal and $X^*$ insulin action on glucose disposal with $p_2^*$ and $p_1^*$ rate constants describing its dynamics and magnitude, respectively. OMM* estimates $R_{\text{a,meal}}$ together with $S_1$ on glucose disposal, with $S_1^*$ defined as:

$$S_1^* = \frac{p_1^*}{p_2^*} \cdot V \left( \text{dL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{per } \mu\text{U/ml} \right)$$

Because OMM* and OMM share $R_{\text{a,meal}}$, the two models were identified simultaneously (see Identification).

Reference-labeled model. The validation of OMM* estimates of $R_{\text{a,meal}}$ and $S_1^*$ was accomplished by using the following rationale. As mentioned in Data, during the labeled meal, two additional tracers were infused intravenously. In particular, [6-3H]glucose was infused to clamp the ratio between concentrations in plasma of [6-3H]glucose and ingested glucose tracer. This allowed us to derive reliable and virtually model-independent estimates of $R_{\text{a,meal}}$ (4). This estimate, denoted $R_{\text{a,meal}}^\text{ref}$, was used not only as a reference with which OMM* estimate of $R_{\text{a,meal}}$ was compared but also as a known input of a model with the same structure of OMM* (Fig. 3, right):

$$G_{\text{meal}}(t) = - \frac{R_{\text{a,meal}}(t) + R_{\text{a,meal}}^\text{ref}(t)}{V_{\text{p}}} \quad G_{\text{meal}}(0) = 0$$

which becomes

$$
\begin{align*}
G_{\text{meal}}(t) &= - \left[ S_G^* + X^*(t) \right] \cdot G_{\text{meal}}(t) + \frac{R_{\text{a,meal}}(\alpha, t)}{V_{\text{p}}} \quad G_{\text{meal}}(0) = 0 \\
X^*(t) &= R_{\text{a,meal}}^\text{ref}(t) + X^*(t) + p_1^* \cdot [I(t) - I_0] \quad X^*(0) = 0
\end{align*}
$$

By identifying this model, denoted as reference-labeled model (RM*), from $G_{\text{meal}}$ and insulin data we were able to obtain reference values for OMM* parameters (indicated by $\text{ref}$), in particular for $S_G^*$ (see Identification). Comparison between $S_1^*$, estimated with RM*, and $S_1^*$ provided by OMM*, allowed OMM* validation.

IVGTT* minimal models. IVGTT* data were interpreted with the classic single-compartment IVMM (5) and with the labeled two-compartment minimal models (IVMM*) (14), thus obtaining an estimate of $S_1$ and $S_1^*$ in the same subjects. This, in addition to providing a one-to-one comparison of IVGTT* $S_1^*$ vs. OMM* $S_1^*$, allows us to examine the relationship between $S_1$ and $S_1^*$ in IVGTT and meal.

Identification

Identifiability. Because OMM* (like OMM) is a priori nonidentifiable, the a priori knowledge necessary for its identification was obtained from RM*. OMM* was thus identified by fixing $V_{\text{p}}$ and $S_G^*$ to the mean values obtained with RM*, i.e., $V_{\text{p}} = V_{\text{p}}^\text{ref}$, $S_G^* = S_G^\text{ref}$. Mean values can safely be used because they are normally distributed (see RESULTS). At variance with OMM, where a Bayesian prior on $p_2$ was needed to improve numerical identifiability, OMM* takes advantage of the fact that it shares $R_{\text{a,meal}}$ with OMM. The simultaneous identification of OMM* and OMM from two measurements ($G_{\text{meal}}$ and $G$) relaxes the necessity of using Bayesian priors for $p_2$ and $p_1^*$. A constraint (11, 12) was imposed to guarantee that the area under the estimated $R_{\text{a,meal}}$ equals the total amount of ingested glucose, $D$, multiplied by the fraction that is actually absorbed, $f$. Because $f$-values estimated with RM* were not normally distributed (RESULTS), $f$ was...
fixed to the median of $RM^*$: $f = f^{m-ref}$. Finally, oral tracer measurements provided information as to when $Ra_{meal}$ began to rise in each subject. If tracer concentration is zero up to time $t_1$, then one can safely assume that $Ra_{meal}$ is zero up to $t_1$.

**Parameter estimation.** All models were numerically identified by nonlinear least squares (7, 9), as implemented in SAAM II [Simulation Analysis and Modeling software (2)]. Measurement error was modeled as normally distributed (9.64 vs. 9.24 $\times$ 10$^{-4}$ dL$^{-1}$ min$^{-1}$ per $\mu$L/ml). To quantify how sensitive the OMM/OMM* estimate of $S_I$ and the percentage deviation of $V, S_{*G}, S_{*G},$ and $f$ were, we used multiple regression analysis between the percentage deviation of $S_I$ and the percentage deviation of $V, S_{*G},$ and $f (V_{*G}, S_{*G})$. We found that the percentage deviations of $f$ and $S_{*G}$ explain the deviation in $S_I$ estimate (0.685, $P < 0.0001$), although the deviation of $V$ doesn’t contribute significantly to the regression. Conversely, the percentage deviations of $f$ and $S_{*G}$ explain the deviation in $S_I$ estimate (0.747, $P < 0.0001$).

**RESULTS**

Parameter estimates of $RM^*$, OMM*, and OMM (simultaneously identified), IVMM*, and IVMM are shown in Table 1 (means $\pm$ SE) with their precision in parentheses (% coefficient of variation). $RM^*$, reference tracer model; OMM*, labeled version of oral glucose minimal model; OMM, oral glucose minimal model; IVMM*, labeled two-compartment intravenous minimal model; IVMM, intravenous minimal model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$S_G$, min$^{-1}$</th>
<th>$S_f$, 10$^{-4}$ dL$^{-1}$ min$^{-1}$ per $\mu$L/ml</th>
<th>$V$, dL/kg</th>
<th>$p_2$, min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$RM^*$</td>
<td>0.0118 $\pm$ 0.0004 (25)</td>
<td>9.24 $\pm$ 0.63 (22)</td>
<td>1.60 $\pm$ 0.04 (8)</td>
<td>0.039 $\pm$ 0.004 (36)</td>
</tr>
<tr>
<td>OMM*</td>
<td>0.0118†</td>
<td>9.64 $\pm$ 0.80 (12)</td>
<td>1.60†</td>
<td>0.043 $\pm$ 0.005 (46)</td>
</tr>
<tr>
<td>OMM</td>
<td>0.025†</td>
<td>12.24 $\pm$ 0.68 (8)</td>
<td>1.45†</td>
<td>0.011 $\pm$ 0.004 (21)</td>
</tr>
<tr>
<td>OMM (separately identified)</td>
<td>0.025†</td>
<td>11.68 $\pm$ 0.3 (7)</td>
<td>1.45†</td>
<td>0.011 $\pm$ 0.005 (15)</td>
</tr>
<tr>
<td>IVMM*</td>
<td>0.0073 $\pm$ 0.0003 (21)</td>
<td>11.59 $\pm$ 0.88 (15)</td>
<td>1.08 $\pm$ 0.03 (14)</td>
<td>0.101 $\pm$ 0.007 (35)</td>
</tr>
<tr>
<td>IVMM</td>
<td>0.019 $\pm$ 0.0004 (32)</td>
<td>6.91 $\pm$ 0.46 (12)</td>
<td>1.62 $\pm$ 0.02 (5)</td>
<td>0.033 $\pm$ 0.002 (16)</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE, with their precision in parentheses (% coefficient of variation). $RM^*$, reference tracer model; OMM*, labeled version of oral glucose minimal model; OMM, oral glucose minimal model; IVMM*, labeled two-compartment intravenous minimal model; IVMM, intravenous minimal model. †Parameters fixed to reference values.

### Table 1. Parameter estimates of $RM^*$, OMM*, and OMM (simultaneously identified), IVMM*, and IVMM

$OMM^*$ vs. $RM^*$. A good agreement was found between $OMM^*$ $R_{meal}$ and $R_{meal}$ (Fig. 4). $S_I^*$ provided by $OMM^*$ and $S_I^*$ were well correlated ($r = 0.80$, $P < 0.0001$; Fig. 5A), and their mean values were not significantly different (9.64 vs. 9.24 $\times$ 10$^{-4}$ dL$^{-1}$ min$^{-1}$ per $\mu$L/ml). To quantify how sensitive the OMM/OMM* estimate of $S_I$ and the assumptions made on $V, S_{*G}, S_{*G},$ and $f$ were, we used multiple regression analysis between the percentage deviation of $S_I$ and the percentage deviation of $V, S_{*G},$ and $f (V_{*G}, S_{*G})$. We found that the percentage deviations of $f$ and $S_{*G}$ explain the deviation in $S_I$ estimate (0.685, $P < 0.0001$), although the deviation of $V$ doesn’t contribute significantly to the regression. Conversely, the percentage deviations of $f$ and $S_{*G}$ explain the deviation in $S_I$ estimate (0.747, $P < 0.0001$).

$OMM^*$ vs. IVMM*. Correlation between IVMM* and $OMM^*$ $S_I^*$ was significant ($r = 0.67$, $P < 0.0001$; Fig. 5B) but their values were significantly different (9.64 vs. 11.59 10$^{-4}$ dL$^{-1}$ min$^{-1}$ per $\mu$L/ml).

$S_I$ vs. $S_I^*$. The relationship between $S_I$ and $S_I^*$ is different during meal and IVGTT. With the oral minimal models, one had 12.24 vs. 9.64 $\times$ 10$^{-4}$ dL$^{-1}$ min$^{-1}$ per $\mu$L/ml, with $S_I > S_I^*$ in 81% of the subjects, although for the IVGTT $S_I$ was lower than $S_I^*$ on average ($S_I = 6.91$ vs. $S_I^* = 11.59$ 10$^{-4}$ dL$^{-1}$ min$^{-1}$ per $\mu$L/ml) and was so in ~90% of the subjects.

### DISCUSSION

The OMM method was developed to measure $S_I$ under physiological conditions, e.g., a meal or OGTT (12). In addi-
Fig. 5. OMM* insulin sensitivity (S*I): correlation with S*I estimated from RM* (A) and from IVMM* (B).

However, from Fig. 5, differences exist at the individual level, thus indicating that OMM* is more robust in population rather than individual studies.

The addition of a tracer to the meal, besides allowing segregation of exogenous component, Gmeal, of plasma glucose concentration G, and thus estimation of insulin sensitivity on glucose disposal, also has beneficial effects on the numerical identifiability of OMM* (and OMM). In fact, OMM*, which is based on Gmeal data, shares Ra meal with OMM, which is based on G data. Thus, for its identification, the unlabeled plasma glucose concentration data G can also be exploited by simultaneously identifying OMM. By doing so, the number of available data doubles, although the number of parameters increases by only two (i.e., from 10 parameters with OMM* alone to 12 with both OMM* and OMM). The improvement in numerical identifiability allowed estimation of p2* and p2 in each individual without having to resort to Bayesian priors as in Refs. 11 and 12. However, parameters V, V*, S*, G*, and f still need to be fixed to population values derived from the reference model. To quantify how sensitive the OMM/OMM* estimate of S1 and S*I to the assumptions made on these parameters were, we investigated, by multiple regression analysis, the relationship between their percentage deviation and that of S1 and S*I. We found that the percentage deviations of f and S*G, explain the deviation in S*I estimate (0.685, P = 0.0001), whereas the deviation of V doesn’t contribute significantly to the regression. The percentage deviations of f, S*, and V* from the fixed values explain the deviation in S*I estimate (0.747, P < 0.0001).

It is of interest to compare S*I with OMM* and IVGTT*. The two estimates showed a significant correlation, r = 0.67, P < 0.0001 (Fig. 5B), although the latter measure was significantly higher: 11.59 vs. 9.64 × 10⁻⁴ dl·kg⁻¹·min⁻¹ per μU/ml. This relationship between the cold and hot estimates of S1 in IVGTT vs. meal is worth commenting on. The IVGTT results observed in the present 88 subjects are consistent with those previously reported in smaller-size studies (8, 10, 14). S1 was lower than S*I in ~90% of the subjects: S1 = 6.91 × 10⁻⁴ vs. S*I = 11.59 × 10⁻⁴ dl·kg⁻¹·min⁻¹ per μU/ml. This relationship is clearly unphysiological, because S1 measures the overall effect of insulin on both glucose disposal and production, whereas S*I measures only the effect of insulin on disposal; by definition, S1 should be equal to or greater than S*I. Possible reasons for this unexpected pattern have been discussed in Ref. 8. The relationship between S1 and S*I improves dramatically with the OMM, S1 = 12.24 × 10⁻⁴ vs. S*I = 9.64 × 10⁻⁴ dl·kg⁻¹·min⁻¹ per μU/ml, with S1 > S*I in 81% of the subjects. However, S1 was still less than S*I in 19% of the subjects. It is likely that the improved performance of the oral minimal models stems from the fact that the minimal model assumptions are more tenable during the gentle meal than during the massive IVGTT perturbation, particularly those concerning the description of how NHGB is controlled by glucose and insulin, which are embodied in both cold models. However, the finding that S*I was greater than S1 in 19% of the subjects also calls for a revision of this functional description for a meal perturbation.

A comment on the relationship between p2 and p2* in IVGTT and meal, as well as on the difference between intravenous and oral values, is also in order. During both IVGTT and meal, p2
is approximately one-third of \( p^*_2 \) (Table 1). This means that insulin action on the liver has a slower dynamic than insulin action on glucose utilization, and, in all likelihood, the underlying assumption of the classic minimal model, that insulin action on glucose production has the same dynamics of insulin action on glucose utilization, is probably not entirely correct. Moreover, the difference found in \( p_2 \) and \( p^*_2 \) values during IVGTT and meal can be explained by considering the differences between the two tests. During IVGTT, glucose and insulin explore a wider range of values than during the meal (G: 90–300 vs. 90–170 mg/dl; I: 4–120 vs. 4–60 \( \mu \)U/ml), thus possibly uncovering some parameter nonlinearities (1, 13).

In conclusion, OMM* provides a means of assessing both \( R_{a,meal} \) and \( S^*_a \) after the ingestion of a carbohydrate-containing meal. Because OMM is simultaneously identified, this approach also permits assessment of the overall effect of insulin on glucose production and disposal (\( S_I \)). Furthermore, when the labeled and unlabeled oral minimal models are combined with the oral C-peptide minimal model (6, 15), insulin secretion and \( \beta \)-cell function indexes can also be measured at the same time. However, although in the present study good performance of the method was observed in a wide range of glucose tolerance (\( S_I \): \( 1.52 \div 30.40 \times 10^{-4} \) dl·kg\(^{-1}\)·min\(^{-1}\) per \( \mu \)U/ml), further studies in diabetic individuals with abnormalities in insulin secretion and action of various degrees of severity are needed to better define the domain of validity of the model. Finally, because insulin action appears to be dependent on the pattern of insulin (1, 13), future studies will be required to determine whether the ability of insulin to stimulate glucose uptake and suppress glucose production in the presence of the continuously changing insulin concentrations observed after a meal is the same as that observed in the presence of different insulin profiles (e.g., during a hyperinsulinemic clamp).

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