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Chiara Dalla Man, Gianna Toffolo, Rita Basu, Robert A. Rizza and Claudio Cobelli
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Claudio Cobelli, Gianna Maria Toffolo, Chiara Dalla Man, Marco Campioni, Paolo Denti, Andrea Caumo, Peter Butler and Robert Rizza
Am J Physiol Endocrinol Metab, July 1, 2007; 293 (1): E1-E15.
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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 Cobelli[1]

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

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 ($R_{a\ meal}^{ref}$) 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 ($R_{a\ meal}$) but also accurately measures S_I^*. We do so by comparing OMM* $R_{a\ meal}$ with the model-independent $R_{a\ meal}^{ref}$ 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 $R_{a\ meal}^{ref}$, 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 ($R_{a\ meal}$) (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 glucose tracer 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 $R_{a\ meal}$. 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 ($R_{a\ meal}^{ref}$) (4). $R_{a\ meal}^{ref}$ 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 $R_{a\ meal}$ to S_I^{*ref} and $R_{a\ meal}^{ref}$, 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 1 ± 0.02 g/kg glucose. The meal was labeled with [1-^{13}C]glucose (G*), thus allowing us to derive the exogenous, i.e, coming from the meal, glucose (G_{meal}) as

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

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-^{3}H]glucose was infused intravenously at a variable rate, mimicking $R_{a\ meal}$. [6,6-^{2}H$_2$]glucose was also infused as part of a separate protocol. Because the ratio in plasma between [6-^{3}H]glucose and [1-^{13}C]glucose was maintained almost constant (Fig. 2*A*), Steele's model provided an essentially model-independent estimate of the R_a of ingested tracer ($R_{a\ meal}^{*\ ref}$) (4); total $R_{a\ meal}^{ref}$ was then calculated from $R_{a\ meal}^{*\ ref}$ (Fig. 2*B*) as
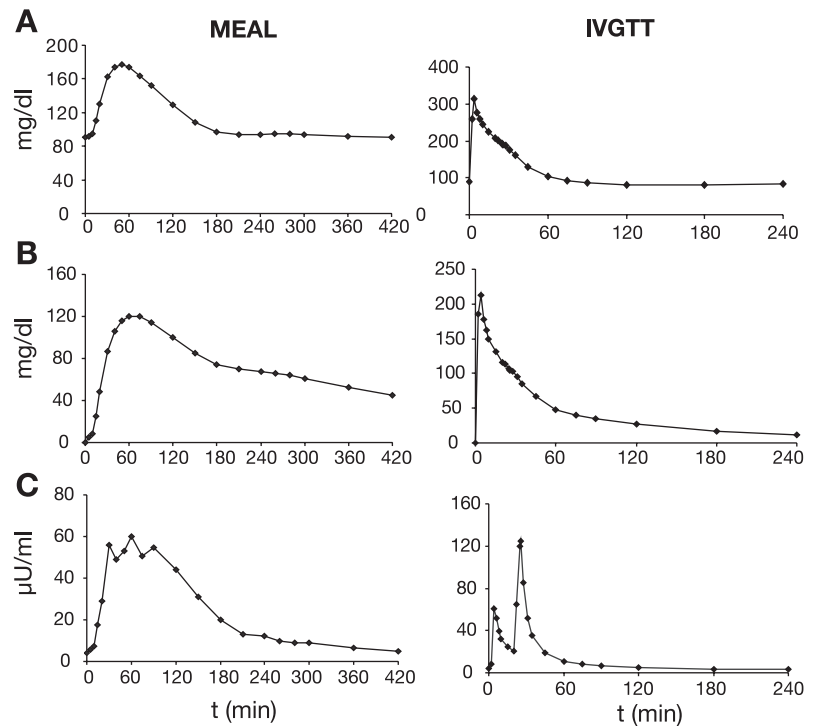
$$R_{a\ meal}^{ref} = R_{a\ meal}^{*\ ref} \cdot \left[1 + \frac{1}{z_{meal}} \right] \quad (2)$$

Labeled intravenous glucose tolerance test. The IVGTT* consisted of a 330 mg/kg glucose bolus at *time 0* labeled with [6,6-^{2}H$_2$]glucose,

Fig. 1. Mean concentration of plasma glucose, exogenous glucose, and insulin during meal (*left*) and intravenous glucose tolerance test (IVGTT; *right*) in normal subjects ($n = 88$).

Fig. 2. Clamped tracer-to-tracee ratio [6-³H]glucose/[1-¹³C]glucose (*A*) and model-independent reference of the rate of appearance of tracer glucose ($R_{a \, meal}^{ref}$; *B*).

followed by a short insulin infusion of 0.02 U/kg between 20 and 25 min. Plasma samples were collected at −120, −30, −20, −10, 0, 2, 4, 6, 8, 10, 15, 20, 22, 25, 26, 28, 31, 35, 45, 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, $R_{a \, meal}$. Denoting by G the total plasma glucose concentration, the rate of glucose disappearance (R_d) and the net hepatic glucose balance (NHGB) (Fig. 3, *left*) model equation following Ref. 5 is

$$\dot{G}(t) = \frac{- R_d(t) + NHGB(t) + R_{a \, meal}(t)}{V}; \quad G(0) = G_b \qquad (3)$$

where *V* is the distribution volume.

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

$$\begin{cases} \dot{G}(t) = - [S_G + X(t)] \cdot G(t) + S_G \cdot G_b + \dfrac{R_{a \, meal}(\boldsymbol{\alpha},t)}{V} & G(0) = G_b \\ \dot{X}(t) = - p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] & X(0) = 0 \end{cases}$$
$$(4)$$

where S_G 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. $R_{a \, meal}$ is described as a piecewise-linear function with known break point t_i and unknown amplitude α_i:

$$R_{a \, meal}(\boldsymbol{\alpha},t)$$
$$= \begin{cases} \alpha_{i-1} + \dfrac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}} (t - t_{i-1}) & per \; t_{i-1} \le t \le t_i \quad i = 1 \dots 8 \\ 0 \end{cases} \qquad (5)$$

with $\boldsymbol{\alpha}$ denoting $[\alpha_1, \alpha_2, \dots \alpha_8]^T$.
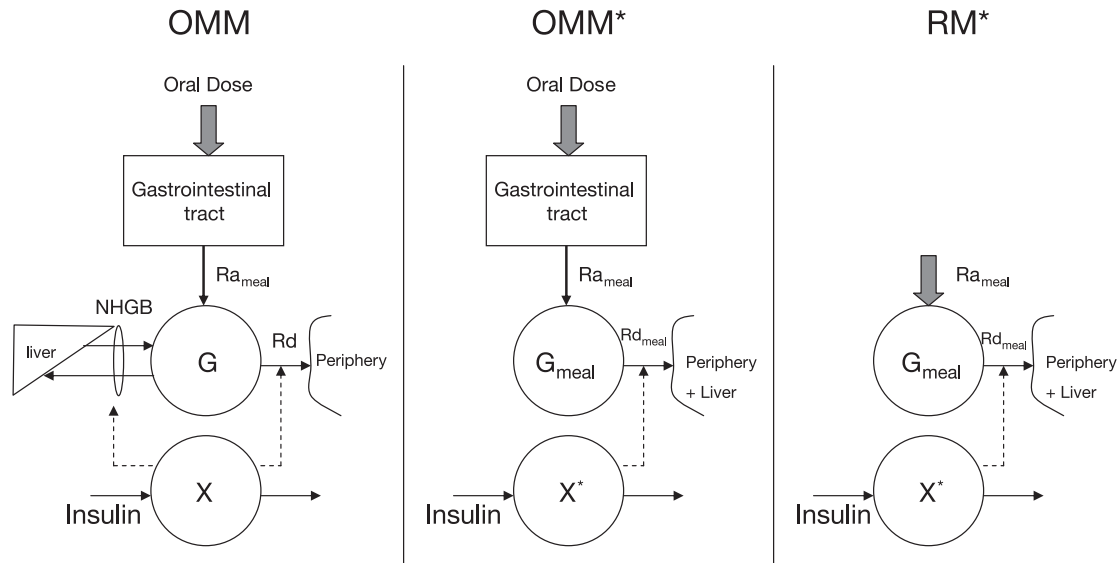
OMM

OMM*

RM*

Fig. 3. *Left*: oral minimal model (OMM). *Middle*: labeled oral minimal model (OMM*). *Right*: reference-labeled model (RM*). In OMM and OMM*, $R_{a\ meal}$ is described with a parametric model, which must be identified from the data. In RM*, input is model independent $R_{a\ meal}^{ref}$, reconstructed by tracer-to-tracee clamp technique.

S_I is given by

$$S_1 = \frac{p_3}{p_2} \cdot V \ (dl \cdot kg^{-1} \cdot min^{-1} \ per \ \mu U/ml) \qquad (6)$$

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_{meal} (eq. 1), and model equation is

$$\dot{G}_{meal}(t) = \frac{-R_{d\ meal}(t) + R_{a\ meal}(t)}{V^*}; \quad G_{meal}(0) = 0 \qquad (7)$$

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

$$\begin{cases} \dot{G}_{meal}(t) = -[S_G^* + X^*(t)] \cdot G_{meal}(t) + \dfrac{R_{a\ meal}(\alpha,t)}{V^*} & G_{meal}(0) = 0 \\ \dot{X}^*(t) = -p_2^* \cdot X^*(t) + p_3^* \cdot [I(t) - I_b] & X^*(0) = 0 \end{cases}$$
$$(8)$$

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_3^* rate constants describing its dynamics and magnitude, respectively. OMM* estimates $R_{a\ meal}$ together with S_I on glucose disposal, with S_I^* defined as:

$$S_1^* = \frac{p_3^*}{p_2^*} \cdot V \ (dl \cdot kg^{-1} \cdot min^{-1} \ per \ \mu U/ml) \qquad (9)$$

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

Reference-labeled model. The validation of OMM* estimates of $R_{a\ meal}$ and S_I^* 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 $R_{a\ meal}$ (4). This estimate,

denoted $R_{a\ meal}^{ref}$, was used not only as a reference with which OMM* estimate of $R_{a\ meal}$ was compared but also as a known input of a model with the same structure of OMM* (Fig. 3, *right*):

$$\dot{G}_{meal}(t) = \frac{-R_{d\ meal}^{ref}(t) + R_{a\ meal}^{ref}(t)}{V^{*ref}}; \quad G_{meal}(0) = 0 \qquad (10)$$

which becomes

$$\begin{cases} \dot{G}_{meal}(t) = -[S_G^{*\ ref} + X^{*\ ref}(t)] \cdot G_{meal}(t) + \dfrac{R_{a\ meal}^{ref}(t)}{V^{*\ ref}} & G_{meal}(0) = 0 \\ \dot{X}^{*\ ref}(t) = p_2^{*\ ref} \cdot X^{*\ ref}(t) + p_3^{*\ ref} \cdot [I(t) - I_b] & X^{*\ ref}(0) = 0 \end{cases}$$
$$(11)$$

By identifying this model, denoted as reference-labeled model (RM*), from G_{meal} and insulin data we were able to obtain reference values for OMM* parameters (indicated by *ref*), in particular for $S_I^{*\ ref}$ (see *Identification*). Comparison between $S_I^{*\ ref}$, estimated with RM*, and S_I^*, 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_I and S_I^* in the same subjects. This, in addition to providing a one-to-one comparison of IVGTT* S_I^* vs. OMM* S_I^*, allows us to examine the relationship between S_I and S_I^* 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^* and S_G^* to the mean values obtained with RM*, i.e., $V^* = V^{*\ ref}$, $S_G^* = S_G^{*\ ref}$. 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 $R_{a\ meal}$ with OMM. The simultaneous identification of OMM* and OMM from two measurements (G_{meal} and G) relaxes the necessity of using Bayesian priors for p_2 and p_2^*. A constraint (11, 12) was imposed to guarantee that the area under the estimated $R_{a\ meal}$ 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

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

	S_G, min^{-1}	S_I, 10^{-4} dl·kg^{-1}·min^{-1} per μU/ml	V, dl/kg	p_2, min^{-1}
RM*	0.0118±0.0004 (25)	9.24±0.63 (22)	1.60±0.04 (8)	0.039±0.004 (36)
OMM*	0.0118†	9.64±0.80 (12)	1.60†	0.043±0.005 (46)
OMM	0.025†	12.24±0.68 (8)	1.45†	0.011±0.004 (21)
OMM (separately identified)	0.025†	11.68±0.3 (7)	1.45†	0.011±0.005 (15)
IVMM*	0.0073±0.0003 (21)	11.59±0.88 (15)	1.08±0.03 (14)	0.101±0.007 (35)
IVMM	0.019±0.0004 (32)	6.91±0.46 (12)	1.62±0.02 (5)	0.033±0.002 (16)

Values are means ± SE, with their precision in parantheses (% 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.

fixed to the median of RM*: $f = f^{\text{m-ref}}$. Finally, oral tracer measurements provided information as to when $R_{a\ meal}$ began to rise in each subject. If tracer concentration is zero up to time t_i and is different from zero at time t_{i+1}, then one can safely assume that $R_{a\ meal}$ is zero up to t_i.

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 assumed to be independent, gaussian, with zero mean and known constant standard deviation. Insulin concentration is the model-forcing function and is assumed to be known without error.

Statistical Analysis.

Data are presented as means ± SE. Two-sample comparisons were done by Wilcoxon signed rank test, and a Shapiro-Wilk test was used to verify whether parameters were normally distributed (significance level set to 5%). Pearson's correlation was used to evaluate univariate correlation.

RESULTS

Parameter estimates of RM*, OMM*, and OMM (simultaneously identified), IVMM*, and IVMM are shown in Table 1 (means ± SE) with their precision.

RM*. RM* parameters were estimated with good precision, and their mean values are $S_G^{*\text{ref}} = 0.0118$ min^{-1}, $V^{*\text{ref}} = 1.60$ dl/kg, $p_2^{*\text{ref}} = 0.039$ min^{-1}, and $S_I^{*\text{ref}} = 9.24 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per μU/ml. The fraction of ingested glucose that reaches plasma, calculated as the ratio between area under $R_{a\ meal}^{\text{ref}}$ and ingested dose, was $f^{\text{ref}} = 0.89$. Parameters $S_G^{*\text{ref}}$, $V^{*\text{ref}}$ were normally distributed (*P* values not significant by Shapiro-Wilk test), although f^{ref} was not (median value $f^{\text{m-ref}} = 0.90$).

OMM* and OMM. The mean profile of $R_{a\ meal}$, reconstructed by simultaneously identifying OMM* and OMM, is shown in Fig. 4. Of note, $R_{a\ meal}$ was virtually superimposable (data not shown) to that reconstructed by identifying OMM alone (11).

OMM* and OMM parameters were $S_I^* = 9.64 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per μU/ml, $p_2^* = 0.043$ min^{-1}, $S_I = 12.24 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per μU/ml, and $p_2 = 0.011$ min^{-1}. This estimate of S_I was not significantly different from that obtained in *Eq. 11* by fitting OMM to total glucose concentration alone, where we found $S_I = 11.68 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per μU/ml. The correlation between the two sets of S_I estimates is very high: $r = 0.96$, $P < 0.001$.

IVMM* and IVMM. S_I^* and S_I were 11.59 and 6.91 10^{-4} dl·kg^{-1}·min^{-1} per μU/ml, respectively.

OMM* vs. RM*. A good agreement was found between OMM* $R_{a\ meal}$ and $R_{a\ meal}^{\text{ref}}$ (Fig. 4). S_I^* provided by OMM* and $S_I^{*\ \text{ref}}$ were well correlated ($r = 0.80$, $P < 0.0001$; Fig. 5A), and their mean values were not significantly different (9.64 vs. 9.24×10^{-4} dl·kg^{-1}·min^{-1} per μU/ml). To quantify how sensitive the OMM/OMM* estimate of S_I and S_I^* to the assumptions made on V, V^*, S_G, S_G^*, and f were, we used multiple regression analysis between the percentage deviation of S_I (S_I^*) and the percentage deviation of V, S_G, and f (V^*, S_G^*, f). 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, S_G^*, and V^* 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·kg^{-1}·min^{-1} per μU/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. 9.64×10^{-4} dl·kg^{-1}·min^{-1} per μU/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. $S_I^* = 11.59 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per μU/ml) and was so in ∼90% of the subjects.

DISCUSSION

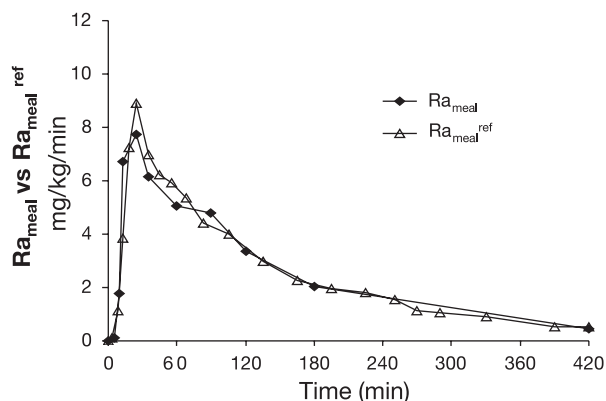The OMM method was developed to measure S_I under physiological conditions, e.g., a meal or OGTT (12). In addi-

Fig. 4. $R_{a\ meal}$ reconstructed by OMM* is shown against $R_{a\ meal}^{\text{ref}}$ of Fig. 2B.
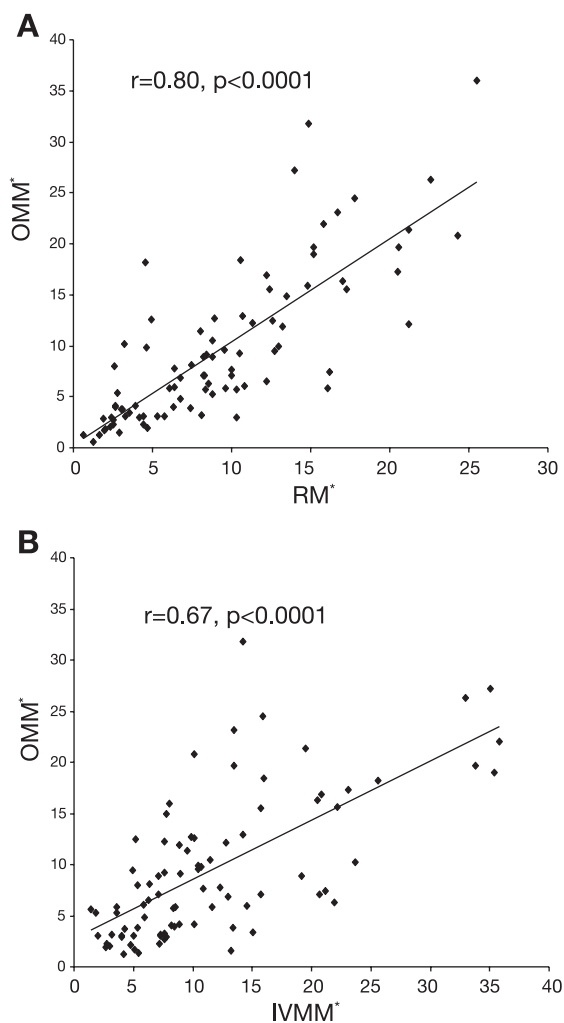
Fig. 5. OMM* insulin sensitivity (S_I^*): correlation with S_I^* estimated from RM* (*A*) and from IVMM* (*B*).

tion, OMM can simultaneously estimate the R_a in plasma of the ingested glucose, $R_{a\ meal}$. The validity of OMM S_I and $R_{a\ meal}$ was recently established (11). However, OMM S_I, although it is an extremely useful index, is a composite measure of insulin action on both glucose production and disposal. Our goal here was to develop a method that specifically measured the ability of insulin to stimulate glucose disposal in physiological conditions. To do this, a tracer was added to the meal, and a labeled OMM (OMM*) was developed. The validity of OMM* S_I^* and $R_{a\ meal}$ was assessed by comparing these values to reference values $S_I^{*\ ref}$ and $R_{a\ meal}^{ref}$, obtained in the same 88 subjects by means of multiple tracer infusions (4). In addition, S_I^* calculated with OMM* was compared with that obtained from a labeled insulin-modified IVGTT (IVGTT*) performed in the same 88 individuals.

The $R_{a\ meal}$ profile obtained with OMM* was very similar to $R_{a\ meal}^{ref}$ (Fig. 4). This is an important result, because due to the experimental conditions (i.e., a tracer-to-tracee clamp), $R_{a\ meal}^{ref}$ provided an essentially model-independent measure of the glucose R_a. S_I^* obtained by OMM* was also very similar to reference values: $S_I^* = 9.64 \pm 0.80 \times 10^{-4}$ vs. $S_I^{*ref} = 9.24 \pm 0.63 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per µU/ml, with a satisfactory correlation between the two ($r = 0.80$, $P < 0.0001$; Fig. 5*A*).

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, G_{meal}, 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 G_{meal} data, shares $R_{a\ meal}$ 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 p_2^* and p_2 in each individual without having to resort to Bayesian priors as in Refs. 11 and 12. However, parameters V, V^*, S_G, 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 S_I 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 S_I 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_G^*, 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. 5*B*), although the latter measure was significantly higher: 11.59 vs. 9.64 $\times 10^{-4}$ dl·kg^{-1}·min^{-1} per µU/ml.

The relationship between the cold and hot estimates of S_I 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). S_I was lower than S_I^* in ~90% of the subjects: $S_I = 6.91 \times 10^{-4}$ vs. $S_I^* = 11.59 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per µU/ml. This relationship is clearly unphysiological, because S_I 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, S_I should be equal to or greater than S_I^*. Possible reasons for this unexpected pattern have been discussed in Ref. 8. The relationship between S_I and S_I^* improves dramatically with the OMM, $S_I = 12.24 \times 10^{-4}$ vs. $S_I^* = 9.64 \times 10^{-4}$ dl·kg^{-1}·min^{-1} per µU/ml, with $S_I > S_I^*$ in 81% of the subjects. However, S_I 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 S_I in 19% of the subjects also calls for a revision of this functional description for a meal perturbation.

A comment on the relationship between p_2 and p_2^* in IVGTT and meal, as well as on the difference between intravenous and oral values, is also in order. During both IVGTT and meal, p_2

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 μU/ml), thus possibly uncovering some parameter nonlinearities (1, 13).

In conclusion, OMM* provides a means of assessing both $R_{a\ meal}$ and S_I^* 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 β-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 μU/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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