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doi:10.1152/ajpendo.90340.2008

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Dynamic insulin sensitivity index: importance in diabetes

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Submitted 7 April 2008; accepted in final form 12 November 2009

Address for reprint requests and other correspondence: C. Cobelli, Dipartimento di Ingegneria dell’Informazione, Università degli Studi di Padova, Via Gradenigo, 6/B-35131 Padova, Italy (e-mail: cobelli@dei.unipd.it).

Pillonetto G, Caumo A, Cobelli C. Dynamic insulin sensitivity index: importance in diabetes. Am J Physiol Endocrinol Metab 298: E440–E448, 2010. First published November 17, 2009; doi:10.1152/ajpendo.90340.2008.—The classical minimal model (MM) index of insulin sensitivity, $S_i$, does not account for how fast or slow insulin action takes place. In a recent work, we proposed a new dynamic insulin sensitivity index, $S_p^p$, which is able to take into account the dynamics of insulin action as well. The new index is a function of two MM parameters, namely $S_i$ and $p_2$, the latter parameter governing the speed of rise and decay of insulin action. We have previously shown that in normal glucose tolerant subjects $S_p^p$ provides a more comprehensive picture of insulin action on glucose metabolism than $S_i$. The aim of this study is to show that resorting to $S_p^p$ rather than $S_i$ is even more appropriate when studying diabetic patients who have a low and slow insulin action. We analyzed insulin-modified intravenous glucose tolerance test studies performed in 10 diabetic subjects and mixed meal glucose tolerance test studies exploiting the triple tracer technique in 14 diabetic subjects. We derived both $S_i$ and $S_p^p$ resorting to Bayesian and Fisherian identification strategies. The results show that $S_p^p$ is estimated more precisely than $S_i$ when using the Bayesian approach. In addition, the less labor-intensive Fisherian approach can still be used to obtain reliable point estimates of $S_p^p$ but not of $S_i$. These results suggest that $S_p^p$ yields a comprehensive, precise, and cost-effective assessment of insulin sensitivity in subjects with impaired insulin action like impaired glucose tolerant subjects or diabetic patients.

The minimal model (MM) of glucose kinetics has been used in nearly 600 papers since its inception in the late seventies (4). The reason for such popularity is related to the ability of MM to provide an index of insulin sensitivity, denoted by $S_i$, from the analysis of an intravenous glucose tolerance test (IVGTT). An extension of this model is being currently used also to determine $S_i$ from an oral/meal glucose tolerance test (OGTT/MGTT; Ref. 8).

Albeit of paramount importance, it must be recognized that $S_i$ does not yield an exhaustive picture of insulin action. The reason can be more easily grasped by making reference to the assessment of insulin sensitivity with the gold standard method, which is the euglycemic hyperinsulinemic clamp. The clamp-based insulin sensitivity, of which the MM-based $S_i$ is a theoretical counterpart, is measured at the end of the clamp when insulin action is at steady state. However, in those clamp studies that monitored in detail the time course of insulin action from the initial to the final steady state, it became apparent that the speed of rise of insulin action varied considerably among individuals and that such speed was related to the degree of insulin sensitivity measured at steady state (15). This observation indicates that when judging on the individual’s ability to dispose glucose, not only is the maximum excursion of insulin action relevant, but also the dynamics of insulin action plays a role. If this is true during a clamp, a fortiori is true during an IVGTT in which insulin action never attains a plateau and its speed of rise and decay certainly influence the return of glucose to the baseline. For this reason, we proposed a new insulin sensitivity index that, at variance with the classic one, also accounts for the dynamics of insulin action. The new index, denoted by $S_p^D$, is able to account for both the speed and the capacity of response. Thanks to this peculiarity, in Ref. 17 we have shown that in normal glucose tolerant (NGT) subjects $S_p^D$ provides, compared with $S_i$, a more comprehensive picture of insulin action on glucose metabolism. In addition, $S_p^D$ is intrinsically more robust than $S_i$, which makes its identification easier and more reliable with respect to $S_i$.

The aim of the present study is to compare the estimation of $S_i$ and $S_p^D$ in diabetic patients and verify whether in these subjects the assessment of $S_p^D$ produces even greater benefits than in NGT subjects. There are two reasons for this to happen. The first one is related to the notion that not only are diabetic patients insulin resistant, but, according to the above-mentioned euglycemic hyperinsulinemic studies, their insulin action develops at a slower pace than in NGT subjects (1, 15). As a result, in diabetic patients $S_p^D$ should be more capable than $S_i$ to provide a realistic picture of how a diabetic patient is able to handle the glucose challenge. Moreover, $S_p^D$ should be more accurate than $S_i$ in ranking diabetic patients. The second reason why $S_p^D$ is expected to perform better than $S_i$ in diabetic patients is related to the numerical identifiability of the MM in such patients. It is well known that in diabetics the MM identification is difficult because it is often associated with large parameters uncertainties (see Refs. 1, 18, 19, 21). The greater robustness of $S_p^D$ with respect to $S_i$ should ensure that $S_p^D$ is precisely estimated even in those patients in which the estimation of $S_i$ is difficult or impossible.

MATERIALS AND METHODS

Estimates of $S_i$ and $S_p^D$ were obtained in diabetic patients under two different experimental conditions: an insulin-modified IVGTT and a MGTT. The IVGTT studies were performed in 10 type 2 diabetic patients whose characteristics have been already described in Refs. 1 and 19. Briefly, the IVGTT consisted of a glucose dose of 300 mg/kg injected at time 0 followed by a short insulin infusion (0.05 U/kg) administered between 20 and 25 min. The MGTT studies were performed in 14 type 2 diabetic subjects who underwent a mixed meal test in which three tracers were simultaneously infused to allow an accurate determination of the rate of appearance of the orally administered glucose into the circulation (see Ref. 3 for details about the experimental protocol and the subjects’ characteristics). The protocol was approved by The Mayo Clinic Institutional Review Board.
To compare the ability of $S_1$ and $S_0$ to discriminate between diabetic and NGT subjects, we performed a simulation study. Estimates of $S_1$ and $S_0$ were obtained from synthetic insulin modified IVGTT experiments performed in 1,000 diabetic and 1,000 NGT subjects. Synthetic data were generated using two log-normal priors for MM parameters. The first prior was obtained from the estimates in diabetic subjects reported in Table 1, while the second prior was derived from the estimates obtained in 10 NGT individuals in a previous study (details are reported in Ref. 17). Then, the typical insulin profile that can be observed during an insulin-modified IVGTT in a diabetic subject was used as the insulin input to the model. We sampled all the generated glucose profiles at 5, 8, 10, 12, 15, 20, 25, 30, 40, 60, 80, 100, 120, 140, 160, 180, and 240 min and finally corrupted them by white normal noise with a coefficient of percentage variation equal to 2.

To validate the new insulin sensitivity index, we used correlation analysis to compare the estimates of $S_0$ obtained in 21 subjects [11 impaired glucose tolerant (IGT) and 10 NGT] undergoing both an OGTT and a euglycemic hyperinsulinemic clamp. Details about the experimental procedures are reported in the Methods in Ref. 9. Here, we just recall that, during the clamp, regular human insulin was infused at a constant rate (25 mU·m⁻²·min⁻¹) for 180 min. A hyperinsulinemic plateau level was achieved within 30–45 min from the initiation of the insulin infusion. Due to the natural variability of the insulin clearance among subjects, the hyperinsulinemic plateau level differed slightly among individuals (means ± SD close to 50 and 10 μU·ml⁻¹, respectively). However, the clamp-based index of insulin sensitivity [$S_i$(clamp)] and the new $S_0$(clamp)], as well as the MM-based indices $S_i$ and $S_0$, have the intrinsic ability to properly account for different hyperinsulinemic levels among individuals (e.g., see Eqs. 2 and 5).

**MM and derivation of dynamic insulin sensitivity.** In the following we refer, without loss of generality, to the MM equations describing glucose disappearance during an IVGTT. The equations describing glucose disappearance during an MGT are the same with the only difference that the exogenous glucose input is the rate of appearance of orally administered glucose that has been accurately estimated thanks to the triple-tracer technique (see Ref. 3 for details). MM equations are as follows:

\[
\begin{align*}
\dot{G}(t) &= - (p_1 + X(t))G(t) + p_G G_0 \quad G(0) = G_0 \quad (1) \\
\dot{X}(t) &= - p_2 X(t) + p_3 (I(t) - I_b) \quad X(0) = 0 \quad (2)
\end{align*}
\]

where $G(t)$ (mg/dl) and $I(t)$ (μU/ml) are glucose and insulin concentrations in plasma, respectively, while $G_0$ and $I_b$ are their baseline values. Equation 1 represents glucose kinetics, whereas Eq. 2 describes insulin action exerted from a compartment remote from plasma. Uniquely identifiable model parameters are $p_1, p_2, p_3, \text{and } G_0$. Parameters of interest provided by the model are glucose effectiveness ($S_i = p_1$, μm⁻¹·min⁻¹), which measures the effect of glucose per se on both glucose disappearance and endogenous glucose production, and insulin sensitivity ($S_i = p_2p_3$, μm⁻¹·min⁻¹·μU⁻¹·ml⁻¹), which measures insulin’s ability to enhance glucose effectiveness by both increasing glucose disappearance and inhibiting endogenous glucose production. Parameter $p_2$ is the time constant of the remote insulin compartment and thus governs the speed of rise and decay of insulin action. Parameters $S_i$ and $p_2$ can be used to derive a dynamic index of insulin sensitivity, as already demonstrated in Ref. 17. For the sake of clarity and completeness, we will briefly state without proof the steps leading to the derivation of $S_0$. The first step consists of obtaining a closed form of the MM glucose prediction, as a function of model parameters and insulin profile. This aim can be accomplished by noticing that Eq. 2 can be integrated independently from Eq. 1. We use $Z(t)$ to denote the integral function of remote insulin. We see from Eq. 2 that the impulse response relation of the deviation from basal and $X(t)$ is $p_1e^{-pt} = S_0 p_2e^{-pt} - S_2 p_2e^{-pt}$ for $\alpha \geq 0$ and zero otherwise. Then $Z(t)$ is the output of a system with impulse response

\[
\int_0^t S_0 p_2 e^{-\alpha p t} \, dt = - S_0 e^{-\alpha p t} |_{t_0}^{t} = S_0 (1 - e^{-\alpha p t}) \cdot \int (I(\alpha) - I_0) \, dt
\]

From a standard result on linear differential equations (see Ref. 6) glucose prediction is given by

\[
G(t) = G_0 e^{-\alpha p t} Z(t) + S_G G_b \int e^{\alpha p t} \alpha p t Z(t) \, dt
\]

Equation 4 allows one to appreciate that, according to the MM, glucose concentration is a function of two signals, i.e., $S_0$ and $Z(t)$. The term $G_0 e^{-\alpha p t} Z(t)$ is a single decaying exponential with a coefficient proportional to the sum of these two signals. In particular, the first of these two signals, i.e., $S_0$, is linearly dependent on glucose effectiveness, $S_i$. The second signal, i.e., $Z(t)$, describes the ability of insulin to enhance glucose effectiveness and depends in a more complex way on both $S_i$ and $p_2$. In fact, from Eq. 3 one can see that $Z(t)$ is the output of a time-invariant linear system having $I(t) - I_b$ as input and $h(t) = S_i(1 - e^{-p_2 t})$ as unit impulse response. This impulse response, denoted by integrated insulin action impulse response (IAIR; Refs. 17, 18), describes the modalities by which incremental (above basal) insulin concentration is able to influence the glucose profile. Dynamic insulin sensitivity, $S_0$, is defined as the mean value of the IAIR in a time interval of duration $T$ (how $T$ is chosen will be clarified in a moment). In mathematical terms, we have:

\[
S_0 = \frac{\int_0^T S_i(1 - e^{-p_2 t}) \, dt}{T} = S_i \left[ 1 - \frac{1 - e^{-p_2 T}}{p_2 T} \right]
\]

It can be verified that $S_0$ is always less or equal to $S_i$. Thus $S_0$ can be conveniently expressed as a fraction, comprised between 0 and 1, of $S_i$. Such fraction is denoted as efficiency.

### Table 1. IVGTT in diabetic subjects: Bayesian estimates of minimal model parameters

<table>
<thead>
<tr>
<th>Subject Nos.</th>
<th>$S_1$, 10⁻⁴ min⁻¹·μU⁻¹·ml⁻¹</th>
<th>$p_2$, 10⁻² min⁻¹</th>
<th>$S_0$, 10⁻⁴ min⁻¹·μU⁻¹·ml⁻¹</th>
<th>$S_c$, 10⁻³ min⁻¹</th>
<th>$G_0$, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 (0.61–2.7)</td>
<td>1.3 (0.13–3.3)</td>
<td>0.3 (0.09–0.65)</td>
<td>1.59 (1.07–1.98)</td>
<td>299.7 (284.1–313.3)</td>
</tr>
<tr>
<td>2</td>
<td>1.5 (1.4–1.6)</td>
<td>7 (5.7–8.4)</td>
<td>0.6 (0.028–0.1)</td>
<td>2.1 (1.8–2.38)</td>
<td>382 (369.9–394.7)</td>
</tr>
<tr>
<td>3</td>
<td>1.7 (0.4–4.1)</td>
<td>0.18 (0.04–0.68)</td>
<td>0.06 (0.028–0.1)</td>
<td>2.1 (0.78–1.35)</td>
<td>434.6 (421.9–448.4)</td>
</tr>
<tr>
<td>4</td>
<td>0.77 (0.58–1.1)</td>
<td>0.8 (0.33–1.3)</td>
<td>0.15 (0.029–0.23)</td>
<td>1.02 (0.76–1.25)</td>
<td>318 (307.4–329.2)</td>
</tr>
<tr>
<td>5</td>
<td>2.1 (1.8–2.2)</td>
<td>9.8 (7.8–12)</td>
<td>0.17 (1.52–1.91)</td>
<td>0.89 (0.48–1.32)</td>
<td>411 (395.6–428.4)</td>
</tr>
<tr>
<td>6</td>
<td>0.39 (0.032–2.3)</td>
<td>0.7 (0.014–7)</td>
<td>0.02 (0.006–0.058)</td>
<td>1.35 (1.16–2.07)</td>
<td>563 (543.3–581.3)</td>
</tr>
<tr>
<td>7</td>
<td>1.51 (0.36–4.1)</td>
<td>0.19 (0.03–3.8)</td>
<td>0.05 (0.03–0.087)</td>
<td>1.48 (1.32–1.62)</td>
<td>314 (304.8–323.5)</td>
</tr>
<tr>
<td>8</td>
<td>0.98 (0.84–1.11)</td>
<td>35 (20–68)</td>
<td>0.93 (0.84–1.06)</td>
<td>0.92 (0.66–1.19)</td>
<td>325.4 (315.3–336.2)</td>
</tr>
<tr>
<td>9</td>
<td>0.8 (0.18–2.7)</td>
<td>0.6 (0.034–2.4)</td>
<td>0.06 (0.018–0.2)</td>
<td>1.61 (1–1.85)</td>
<td>350.9 (335.4–363.2)</td>
</tr>
<tr>
<td>10</td>
<td>0.6 (0.46–0.72)</td>
<td>2.5 (2.1–3)</td>
<td>0.29 (0.22–0.36)</td>
<td>0.84 (0.52–1.18)</td>
<td>263 (252.5–275.2)</td>
</tr>
</tbody>
</table>

Nos. in parentheses show 95% confidence intervals. IVGTT, intravenous glucose tolerance test; $S_i$, insulin sensitivity; $p_2$, rate parameter; $S_0$, dynamic insulin sensitivity index; $S_c$, glucose effectiveness; $G_0$, glucose at time 0.

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DYNAMIC INSULIN SENSITIVITY: A NEW INDEX

η(p2, T) = \frac{S_D}{S_I} = \left[ 1 - \frac{1 - e^{-pT}}{pT} \right] (6)

Efficiency η measures which fraction of the potentially available insulin sensitivity, denoted by S_I, is translated into effective glycemic control by means of a rapid increase of insulin action. The rapidity of insulin action is governed by parameter p_2 and η increases monotonically as a function of p_2 (once T has been fixed). Notice that the closer η to 1, the larger the efficiency of the metabolic system in converting S_I into an effective insulin control on glucose. Conversely, a very low η renders S_D close to zero, i.e., in this case insulin action is virtually unavailable during the experiment. This observation explains why a high S_I value does not necessarily imply an effective control of insulin on glucose, since it can be associated with a low p_2 and thus with a low efficiency.

As far as the choice of T is concerned, such a parameter does not represent the length of the IVGTT but is the duration of a "thought experiment" where insulin action has time to develop and IAIR can be directly observed. The "optimal" value of T should allow η to vary in the largest possible range of values so as to magnify differences between η values of the subjects under study. The reader is referred to Ref. 17 for all the details. Here, we just recall that after considering a wide population of NGT, IGT, and diabetic individuals, a robust scheme, which, albeit less sophisticated than the Bayesian one, makes a maximum likelihood (ML) estimator (2, 7) was adopted. This powerful approach allows one to reconstruct (in sampled form) the entire a posteriori probability density function of SI, thus permitting a more effective comparison of the performance of the new index with respect to the classic one. The Bayesian approach requires a probabilistic description of the a priori knowledge concerning the parameters to be estimated. The MM parameters S_I, S_G, p_2, and G_0 were assumed independent of each other and since all of them are nonnegative, priors whose support extends only in the positive axis were used. The a priori probability density functions of S_G and G_0 were assumed to be uniform in [0, a] with a → +∞. The choice of the a priori probability density function of S_I was based on the information on diabetic subjects reported in literature, e.g., Refs. 16 and 19. Specifically, we assumed for S_I an a priori probability density function where S_I values < 2 × 10^{-3} (min^{-1}μU/ml) are equally probable, whereas S_I values > 2 × 10^{-4} are less and less probable according to a decreasing exponential law (with exponent equal to 10^9 μU/ml^{-1} min). The choice of the a priori probability density function of p_2 was based on the rationale described in Ref. 18; that is, we assumed a uniform distribution in the interval [0.5] min^{-1}. It is worth anticipating that the prior information on the MM parameters did not influence the general conclusions obtained in the study.

The MM was also identified using a Fisher parameter estimation scheme, which, albeit less sophisticated than the Bayesian one, makes it possible the adoption of mode-finding algorithms that are much less demanding than MCMC. This can have practical relevance in large-scale or epidemiological studies in which S_D has to be estimated in many subjects. To carry out the Fisherian estimation of the MM parameters, a maximum likelihood (ML) estimator (2, 7) was adopted.

MM identification: IVGTT data. As already observed in Ref. 3, when the MM is identified from MGTT data, some difficulties arise because the slow changes that glucose and insulin concentrations exhibit under postprandial conditions make it difficult to distinguish the individual contribution of insulin sensitivity and glucose effectiveness to glucose disappearance. To overcome this drawback, we followed the same strategy that was adopted in Ref. 3 to improve the numerical identifiability of the model, i.e., we exploited the fact that S_G, measuring glucose effectiveness at basal insulin, can be factored out in the sum of the glucose effectiveness at zero insulin (GEZI) and the product of insulin sensitivity times basal insulin concentration:

S_G = GEZI + S_Gb (7)

The advantage of expressing S_G in these terms lies in the possibility of introducing some reasonable assumptions about GEZI that guarantee an easier numerical identification of the MM. GEZI was assumed Gaussian with a mean of 0.025 and SD of 0.0025. The MM parameters were estimated by maximizing a penalized likelihood accounting for Eq. 7 and the prior on GEZI. To investigate the sensitivity of the MM estimates to the prior on GEZI, the MM identification was also carried out using a much less informative prior on GEZI (the SD of GEZI was increased from 0.0025 to 0.01).

Estimation of S_D from an OGTT and a euglycemic hyperinsulinemic clamp. We assessed the validity of S_D by comparing its estimates obtained in 21 subjects who underwent both an OGTT and a euglycemic hyperinsulinemic clamp.

OGTT-based estimates of S_D were computed from Eq. 5 using the estimates of S_I and p_2 obtained in Ref. 9. Of note is that the OGTT-based S_D estimate also accounts for the glucose distribution volume, V (see Eq. 7 in Ref. 9).

For what concerns computation of S_D(clamp), we simply refer to the theoretical definition of S_D. During an ideal clamp, the glucose infusion rate, R(t), is proportional to IAIR (see Appendix of Ref. 17) and equals insulin action multiplied by the distribution volume. Thus from Eq. 2 we have:

\[ \hat{R}(t) = -p_2R(t) + V \times p_3(I(t) - I_b) \quad R(0) = 0 \] (8)

Parameters p_2 and V \times p_3 governing the dynamics of R(t) were estimated by fitting the samples of R(t) via nonlinear least squares (the forcing input was defined by linearly interpolating the samples of insulin collected during the clamp). Finally, the dynamic insulin sensitivity was computed as follows:

S_D^{(\text{clamp})} = \frac{Vp_3}{p_2} \left[ 1 - \frac{1 - e^{-pT}}{pT} \right] \text{ with } T = 60 \text{ min} (9)

RESULTS

The MM identification results of the 10 diabetic patients who underwent the IVGTT are reported in Table 1 (Bayesian approach) and Table 2 (Fisherian approach). In particular, Table 1 reports the minimum variance estimates of S_I, p_2, S_D, S_G, and G_0, and the 95% confidence intervals (obtained as the

Table 1. IVGTT in diabetic subjects: maximum likelihood S_I and S_D estimates

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>S_I 10^{-4} min^{-1} μU^{-1} ml</th>
<th>S_D 10^{-4} min^{-1} μU^{-1} ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.92</td>
<td>0.31</td>
</tr>
<tr>
<td>2</td>
<td>1.51</td>
<td>1.16</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
<td>0.029</td>
</tr>
<tr>
<td>4</td>
<td>0.86</td>
<td>0.15</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>1.74</td>
</tr>
<tr>
<td>6</td>
<td>0.14</td>
<td>0.027</td>
</tr>
<tr>
<td>7</td>
<td>0.98</td>
<td>0.046</td>
</tr>
<tr>
<td>8</td>
<td>0.99</td>
<td>0.935</td>
</tr>
<tr>
<td>9</td>
<td>0.52</td>
<td>0.017</td>
</tr>
<tr>
<td>10</td>
<td>0.58</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table 2. IVGTT in diabetic subjects: maximum likelihood S_I and S_D estimates

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>S_I 10^{-4} min^{-1} μU^{-1} ml</th>
<th>S_D 10^{-4} min^{-1} μU^{-1} ml</th>
</tr>
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<tr>
<td>1</td>
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interval between quantiles 2.5 and 97.5%) in parentheses. Table 2 shows the ML estimates of $S_i$ and $S^D_i$. Figure 1 shows the marginal posteriors (obtained in sampled form by MCMC) of the parameters $S_i$, $p_2$, and $S^D_i$ for subjects 2 (top) and 3 (bottom). Figure 2 displays $S_i$ and $S^D_i$ point estimates obtained in all the 10 subjects with 95% confidence intervals. Figure 3 compares $S_i$ (left) and $S^D_i$ (right) estimates obtained using the Fisherian and the Bayesian approach. The correlation coefficient between ML and Bayes estimates of $S_i$ and of $S^D_i$ turns out to be 0.67 and 0.99, respectively.

Table 3 reports the identification results of the 14 diabetic patients who underwent the MGTT. In this table, the estimates of $S_i$, $p_2$, and $S^D_i$ obtained using both the full as well as the less informative prior on GEZI are shown. Figure 4 compares the $S_i$ (left) and $S^D_i$ (right) estimates obtained with the two priors.

Figure 5 reports the results of the simulation study designed to compare the performance of $S_i$ and $S^D_i$ in NGT and diabetic subjects. The true values of $S_i$ and $S^D_i$ are plotted against the values estimated by ML in the two groups. The correlation coefficients between true and estimated $S_i$ are $0.1$ and $0.4$ in diabetic and NGT subjects, respectively, while those concerning $S^D_i$ are $0.98$ and $0.99$, respectively.

Figures 6 and 7 concern the results obtained in the 21 subjects who underwent both an OGTT and a clamp experiment. Figure 6 shows the fit of clamp data in one representative IGT subject: the glucose infusion rate values during the clamp are denoted by the open circles, while the solid line describes the curve, proportional to IAIR, obtained after fitting the samples using Eq. 8 and nonlinear least squares. The area under the curve in the first 60 min (shaded area) is proportional to $S^D_i$(clamp). Figure 7 compares the $S^D_i$(clamp) and $S^D_i$ estimates obtained in the two experimental situations via correlation analysis. In particular, the correlation coefficient between OGTT-based estimate of $S^D_i$ and $S^D_i$(clamp) is 0.82.

**DISCUSSION**

**IVGTT in diabetic subjects: $S_i$ vs. $S^D_i$ using Bayes estimation.** To comment on the results of the Bayesian estimation, it is helpful to examine the MM identification results obtained in two paradigmatic subjects. Figure 1 plots the marginal posteriors (obtained in sampled form by MCMC) of the parameters $S_i$, $p_2$, and $S^D_i$ for subject 2 (top) and 3 (bottom). As far as $S_i$ is concerned (first column of Fig. 1), one can see that this parameter is well estimated in subject 2. In fact, its posterior appears well concentrated around its mean. From Table 1, one can see that the point estimate of $S_i$ is 1.5 (1.4–1.6) in this subject. The situation is completely different for subject 3. In this subject, $S_i$ suffers of poor numerical identifiability, as indicated by its long-tailed marginal posterior (this phenomenon is mathematically explained by Proposition 2 in Ref. 18). In addition, the point estimate of $S_i$ is 1.7 (0.4–4.1) and thus very close to the mean of the prior (whose value is $1.67$). This suggests that the IVGTT data provide little information to estimate $S_i$ in this subject. All in all, it is difficult to tell whether the $S_i$ of subject 3 is really higher than that of subject 2. The examination of the $S^D_i$ results obtained in the same subjects offers a completely different scenario. In fact, the marginal posteriors of $S^D_i$ (third column of Fig. 1), are well concentrated around their means in both subjects. The $S^D_i$ point estimates are 1.17 (1.1–1.23) and 0.06 (0.028–0.1), respectively, and this suggests that insulin is in all likelihood more effective to enhance glucose disappearance in subject 2 than in subject 3. To understand why the point estimate of $S^D_i$ is much...
lower in subject 3 than in subject 2, one must consider that $S^D$ embodies the information brought about by both $S_I$ and $p_2$ (the latter parameter is reported in the second column of Fig. 1). It can be seen that in subject 3 the $S_I$ 95% confidence interval includes many $S_I$ values that are coupled with very low values of $p_2$. This means that in this subject $S_I$ is frequently associated with very low values of the efficiency $\eta$, which translates into a low point estimate of $S^D$.

The usefulness of the new index is also apparent when the whole group of diabetic subjects is considered. The results reported in Fig. 2 displaying the $S_I$ and $S^D$ estimates together with their 95% confidence intervals indicate that $S^D$ never exhibited numerical identifiability problems. In contrast, the $S_I$ results found in subjects 1, 3, 6, 7, and 9 are rather difficult to interpret.

IVGTT in diabetic subjects: Bayes vs. Fisher estimation of $S^D$. In Ref. 19, the Bayes approach was shown to be much more robust than the Fisher one in estimating $S_I$ and $p_2$ in NGT subjects. Bayes superiority over Fisher can be even more appreciated in the present study because diabetic patients exhibit low values of $S_I$ that are often coupled with low values of $p_2$. In this case, the profile of insulin action becomes so low and slow so as to degrade the precision of the MM parameter estimates. In fact, ML often yields an estimate of $S_I$ that is affected by a large uncertainty and cannot be discriminated from zero (this is known in the literature as the “$S_I=0$” problem; Refs. 1, 18, 19). As a consequence, the histogram describing the $S_I$ frequency distribution is bimodal showing an artifactual peak at $S_I=0$ and another peak at a positive $S_I$ value, which leads to interpretative difficulties. Another problem is also that $S_I$ estimates can turn out to be unrealistically high. Bayes estimation, implemented by using MCMC, is more robust than Fisher estimation since it provides a nonzero minimum variance estimate of $S_I$ that hinges on the entire marginal posterior of $S_I$. In addition, rigorous confidence intervals for $S_I$ can be calculated. The question arises as to whether the same results also hold for $S^D$. Since $S^D$ depends on both $p_2$ and $S_I$ (see Eq. 5), one would not be surprised to find...
out that also the Fisherian point estimate of $S_I^D$ is plagued by
the same problem described above for $S_I$. Fortunately, how-
ever, the Fisherian estimate of $S_I^D$ was often very close to the
one obtained with the Bayesian approach. This can be appreci-
ated by looking at Fig. 3 where the Bayesian and Fisherian
estimates of $S_I$ and of $S_I^D$ were reported. As said, the correlation
coefficient between ML and Bayes estimates of $S_I$ and of
$S_I^D$ was 0.67 and 0.99, respectively. This favorable outcome for $S_I^D$
is related with the functional relationships among $S_I$, $p^2$, IAIR,
and $S_I^D$. While it is difficult to estimate precisely $S_I$ and $p^2$, due
to the presence of numerical nonidentifiability regions that
make many different combinations of $S_I$ and $p^2$ capable of
generating virtually the same IAIR on a finite time interval,
IAIR itself and its integral (and thus $S_I^D$) can be precisely
determined. Thus, although Bayes is more robust in estimating
$S_I$ and $p^2$ separately, Bayes and Fisher behave similarly as
regards $S_I^D$.

In summary, the Fisher estimator often provides $S_I^D$ esti-
mates comparable to the Bayesian ones with a reduced com-
putational effort (few seconds in place of minutes, since
Markov chain generation and Monte Carlo integration are more
demanding than mode-finding algorithms). This advantage of
$S_I^D$ over $S_I$ may be particularly relevant in large-scale studies in
which many model identifications must be carried out.

**IVGTT and MGTT in diabetic subjects: sensitivity of $S_I$ and
$S_I^D$ to prior.** To assess the sensitivity of the results to the prior
information on $S_I$ used in the MM Bayesian identification from
IVGTT in diabetics, the estimation process was repeated using
larger thresholds (3 and 4 in place of 2). As already found in
Ref. 19, $S_I$ and $p^2$ were particularly sensitive to prior informa-
tron. In particular, the prior information exerted a profound
influence on the tails of the $S_I$ and $p^2$ marginal posteriors. Quite
the contrary, we found (results not shown) that the new
index $S_I^D$ is scarcely sensitive to the prior information. MM

![Fig. 3. IVGTT. Left: maximum likelihood vs. Bayesian $S_I$ estimates in diabetic subjects. Right: ML vs. Bayesian $S_I^D$ in diabetic subjects.](image)

<table>
<thead>
<tr>
<th>Subject Nos.</th>
<th>$S_I(1)$</th>
<th>$S_I(2)$</th>
<th>$S_I^D(1)$</th>
<th>$S_I^D(2)$</th>
<th>$p^2(1)$</th>
<th>$p^2(2)$</th>
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<tbody>
<tr>
<td>1</td>
<td>5.9</td>
<td>12.2</td>
<td>0.31</td>
<td>0.29</td>
<td>0.18</td>
<td>0.081</td>
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<tr>
<td>2</td>
<td>2.0</td>
<td>2.0</td>
<td>0.41</td>
<td>0.39</td>
<td>0.78</td>
<td>0.758</td>
</tr>
<tr>
<td>3</td>
<td>6.8</td>
<td>6.6</td>
<td>0.73</td>
<td>0.74</td>
<td>0.38</td>
<td>0.404</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>5</td>
<td>0.12</td>
<td>0.11</td>
<td>0.167</td>
<td>0.078</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>4.3</td>
<td>0.16</td>
<td>0.14</td>
<td>0.258</td>
<td>0.116</td>
</tr>
<tr>
<td>6</td>
<td>4.4</td>
<td>6.5</td>
<td>0.349</td>
<td>0.33</td>
<td>0.28</td>
<td>0.177</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>1.38</td>
<td>0.55</td>
<td>0.23</td>
<td>1.7</td>
<td>0.63</td>
</tr>
<tr>
<td>8</td>
<td>6.3</td>
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<td>1.46</td>
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<td>0.92</td>
<td>1.42</td>
</tr>
<tr>
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<td>6.9</td>
<td>6.9</td>
<td>0.72</td>
<td>0.72</td>
<td>0.37</td>
<td>0.377</td>
</tr>
<tr>
<td>10</td>
<td>2.0</td>
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<td>0.015</td>
<td>0.025</td>
<td>0.019</td>
</tr>
<tr>
<td>11</td>
<td>4.6</td>
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<td>0.17</td>
<td>0.17</td>
<td>0.13</td>
<td>0.053</td>
</tr>
<tr>
<td>12</td>
<td>5.8</td>
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<td>0.39</td>
<td>0.26</td>
<td>0.107</td>
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<tr>
<td>13</td>
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<td>0.3</td>
<td>1.07</td>
<td>0.05</td>
</tr>
<tr>
<td>14</td>
<td>24.1</td>
<td>24.3</td>
<td>0.0064</td>
<td>0.0057</td>
<td>0.00088</td>
<td>0.00078</td>
</tr>
</tbody>
</table>

Estimates are denoted by $S_I(1)$, $S_I^D(1)$, and $p^2(1)$ when using the full prior and by $S_I(2)$, $S_I^D(2)$, and $p^2(2)$ when using the less informative prior; GEZI, glucose
effectiveness at zero insulin; MGTT, meal glucose tolerance test; measurement units of MM parameters are the same as in Tables 1 and 2.
identification from MGTT data in the 14 diabetic patients provides further support to these findings. In fact, inspection of Table 3 and Fig. 4 indicate that, at variance with $S_1$ and $p_2$, the estimates of $S_D^1$ are virtually insensitive to the prior information on GEZI.

The reasons for the higher robustness of $S_D^1$ with respect to $S_1$ and $p_2$ are the same already put forth to discuss the Bayesian vs. Fisherian identification results. The parameters $S_1$ and $p_2$ are more sensitive to the prior information because of the existence of numerical nonidentifiability regions in the parameter space where changes in these two parameters only produce negligible changes in the likelihood (18). Within such numerical nonidentifiability regions, many different combinations of $S_1$ and $p_2$ may lead to similar IAIR. Since $S_D^1$ is the mean of IAIR in the interval $(0, T]$ with $T = 60$ min, many different combinations of $S_1$ and $p_2$ are mapped into the same $S_D^1$. Therefore, whereas $S_1$ and $p_2$ may be very uncertain, $S_D^1$ is not.

This peculiarity of $S_D^1$ can be easily grasped by resorting to a clamp thought experiment, where $S_1$ depends on the asymptotic value of the exogenous glucose infusion. Large and unrealistic

![Fig. 4. Meal glucose tolerance test (MGTT). Left: insulin sensitivity using full prior information on glucose effectiveness at zero insulin [GEZI; $S_1(1)$] vs. less informative [$S_1(2)$]. Right: dynamic insulin sensitivity using full prior information on GEZI [$S_D^1(1)$] vs. less informative [$S_D^1(2)$].](image)

![Fig. 5. Left: true $S_1$ vs. estimated $S_1$ in diabetic (top) and NGT subjects (bottom). Right: true $S_D^1$ vs. estimated $S_D^1$ in diabetic (top) and NGT subjects (bottom).](image)
S_{i} values may be obtained in diabetic subjects since they are associated with low $p_{2}$ values that define virtual glucose infusions similar to straight lines, which “almost diverge” at infinity. On the other hand, by definition, $S_{D}$ is proportional to the area of glucose infusion in the first 60 min and it is thus much less sensitive to poor numerical identifiability of $p_{2}$. As a practical consequence, $S_{D}$ can be reliably estimated from IVGTT/MGTT experiments also under conditions where $S_{i}$ and $p_{2}$ suffer from poor numerical identifiability. The small sensitivity of $S_{D}$ to the prior information contributes to make $S_{D}$ a much more robust and objective measure of insulin ability to control glucose.

**IVGTT: $S_{i}$ vs. $S_{D}$ ability in discriminating NGT and diabetic subjects.** The results reported in Fig. 5 provide further support to the notion that $S_{D}$ can be estimated with much more precision than $S_{i}$ during an IVGTT experiment, especially when diabetic subjects are under study. As already said, the correlation coefficients between true and estimated $S_{i}$ are $\sim 0.1$ and 0.4 in diabetic and NGT subjects, respectively, while those concerning $S_{D}$ are 0.98 and 0.99, respectively. It is of interest that in Fig. 5, top left, almost 10% of estimated $S_{i}$ values turn out to be 10 times larger than the true ones. This means that, in a nonnegligible number of cases, a diabetic patient is erroneously classified as a subject with a normal insulin sensitivity. In contrast, the discriminatory power of $S_{D}$ is always excellent. This new evidence of the superior performance of $S_{D}$ against $S_{i}$ adds to the one previously reported in Refs. 17 and 20, where we showed that the new dynamic index is better correlated than $S_{i}$ with the time by which glucose concentration reattains its basal level after a glucose bolus (17). Further, by incorporating the concept of efficiency, the new index provides an elegant answer to those perplexing situations in which, despite an elevated value of $S_{i}$, the rate of glucose disappearance seems to be scarcely affected by insulin. This occurs when the elevated $S_{i}$ cannot be promptly translated into effective insulin action due to a low $p_{2}$ value. This situation is exemplified by the results of *patient 14* in Table 3. In fact, in this subject, the large $S_{i}$ value would suggest that insulin control is in the normal range, whereas the $S_{D}$ value unmasks a low ability to restore glucose homeostasis. The simulation study results reported in Fig. 5 further corroborate the notion that $S_{D}$ can considerably improve the reliability of the assessment of insulin sensitivity in diabetic patients. Furthermore, the issue of the validity of $S_{D}$ against a reference measure has been tackled in the present study by comparing the estimates of $S_{D}$ obtained from an OGTT with those obtained in the same subjects from a euglycemic hyperinsulinemic clamp, i.e., the gold standard technique for the assessment of insulin sensitivity.

Conclusions

The present study is a follow up of previous paper in NGT subjects (17) where we pointed out the limitations of the classical MM index of insulin sensitivity, $S_{i}$, and proposed a novel index, $S_{D}$. The new index yields a more comprehensive picture of insulin’s ability to control glucose metabolism because it hinges upon a theoretically based combination of $p_{2}$ and $p_{3}$ that better accounts for the dynamic properties of insulin action. For instance, $S_{D}$ has been shown to be better correlated than $S_{i}$ with the time by which glucose concentration reattains its basal level after a glucose bolus (17). Further, by incorporating the concept of efficiency, the new index provides an elegant answer to those perplexing situations in which, despite an elevated value of $S_{i}$, the rate of glucose disappearance seems to be scarcely affected by insulin. This occurs when the elevated $S_{i}$ cannot be promptly translated into effective insulin action due to a low $p_{2}$ value. This situation is exemplified by the results of *patient 14* in Table 3. In fact, in this subject, the large $S_{i}$ value would suggest that insulin control is in the normal range, whereas the $S_{D}$ value unmasks a low ability to restore glucose homeostasis. The simulation study results reported in Fig. 5 further corroborate the notion that $S_{D}$ can considerably improve the reliability of the assessment of insulin sensitivity in diabetic patients. Furthermore, the issue of the validity of $S_{D}$ against a reference measure has been tackled in the present study by comparing the estimates of $S_{D}$ obtained from an OGTT with those obtained in the same subjects from a euglycemic hyperinsulinemic clamp, i.e., the gold standard technique for the assessment of insulin sensitivity.

![Fig. 6. Clamp model. Samples of glucose infusion measured in the first IGT subject (circles) and curve (proportional to FAIRR) obtained after fitting the samples using Eq. 8 (solid line). Area under the curve in the first 60 min is proportional to $S_{D}$(clamp).](image1)

Such degree of correlation is almost identical to the one between $S_{i}$ and $S_{D}$(clamp) ($r = 0.81$) obtained from the analysis of the same experimental data in a previous report (9). It is worth noticing that if we focus our attention on the results obtained in the 11 IGT subjects, the correlation index between $S_{i}$ and $S_{D}$(clamp) is 0.91, whereas that between $S_{i}$ and $S_{D}$(clamp) is only 0.7. Instead, in the 10 NGT subjects, the two correlation indexes are similar and $\sim 0.6$. This dissimilarity also points in the direction that the benefits of $S_{D}$ become more and more relevant as the degree of glucose tolerance decreases.
The results of the present study indicate that the new dynamic index is especially useful in those diabetic subjects having a slow timing of insulin action. It is well known that, when analyzing IVGTT data, the estimation of $p_2$ in diabetic subjects is often problematic. One of the most relevant findings of the present study is that $S_D$ is much less affected than $S_I$ by such a drawback. Thus $S_D$ has the additional advantage over $S_I$ in that its estimation is much more robust and can be accomplished by resorting to the Fisher approach. In fact, at variance with what happens with $S_I$, the Fisherian and Bayesian point estimates of $S_D$ are similar, with the latter being virtually insensitive to the prior information incorporated in the estimator. Since ML is much less computationally demanding than MCMC, this makes $S_D$ more appealing than $S_I$ in studies where many subjects have to be analyzed. $S_D$ thus appears particularly suitable to be employed in population studies where glucose intolerant subjects are likely to be present, as well as in studies seeking for diabetes-relevant genes in the human genome (12, 14, 21, 22).

DISCLOSURES

No conflicts of interest are declared by the author(s).

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