Evaluation of Insulin Sensitivity and \( \beta \)-Cell Function Indexes Obtained From Minimal Model Analysis of a Meal Tolerance Test

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Modeling analysis of glucose, insulin, and C-peptide following a meal has been proposed as a means to estimate insulin sensitivity \( (S) \) and \( \beta \)-cell function from a single test. We compared the model-derived meal indexes with analogous indexes obtained from an intravenous glucose tolerance test (IVGTT) and hyperglycemic clamp (HGC) in 17 nondiabetic subjects (14 men, 3 women, aged \( 50 \pm 2 \) years [mean \( \pm \) SE], BMI 25.0 \( \pm \) 0.7 kg/m\(^2\)). \( S \) estimated from the meal was correlated with \( S \) estimated from the IVGTT and the HGC \( (r = 0.59 \text{ and } 0.76, \text{ respectively}; P < 0.01 \text{ for both}) \) but was \(-2.3 \text{ and } 1.4 \text{ times higher} (P < 0.05 \text{ for both}) \). The meal-derived estimate of the \( \beta \)-cell’s response to a steady-state change in glucose (static secretion index) was correlated with the HGC second-phase insulin response \( (r = 0.69; P = 0.002) \), but the estimated rate-of-change component (dynamic secretion index) was not correlated with first-phase insulin release from either the HGC or IVGTT. Indexes of \( \beta \)-cell function obtained from the meal were significantly higher than those obtained from the HGC. In conclusion, insulin sensitivity and \( \beta \)-cell indexes derived from a meal are not analogous to those from the clamp or IVGTT. Further work is needed before these indexes can be routinely used in clinical and epidemiological studies. Diabetes 53:1201–1207, 2004

Establishing a single test that assesses insulin secretion and insulin sensitivity under normal physiologic conditions is potentially of great value for both epidemiological and clinical studies. To this end, a minimal model estimate of insulin sensitivity based on a meal tolerance test has recently been developed by Caumo et al. (1), and several groups (2–10) have proposed model-based methods for assessing \( \beta \)-cell function from arbitrary glucose excursions. The meal-derived estimate of insulin sensitivity \( [S_{\text{MEAL}}] \) has been shown to correlate with that obtained from an intravenous glucose tolerance test (IVGTT) \([S_{\text{IVGTT}}] \) (1), but none of the model-based indexes of \( \beta \)-cell function have been rigorously compared with estimates of first- and second-phase insulin release obtained from standard tests such as the IVGTT (11–13) or hyperglycemic clamp (HGC) (14–16).

To more fully assess whether indexes of insulin sensitivity and \( \beta \)-cell function can both be obtained from a meal test, we measured plasma glucose, insulin, and C-peptide concentrations over a 24-h period. On separate days, an IVGTT and HGC were performed. The IVGTT was used to assess insulin sensitivity \([S_{\text{IVGTT}}]\) and first-phase insulin release \([\Phi_{1\text{IVGTT}}]\). The HGC was used to assess first- \([\Phi_{1\text{HGC}}]\) and second-phase insulin release \([\Phi_{2\text{HGC}}]\) and to obtain an additional estimate of insulin sensitivity \([S_{\text{HGC}}] \). These estimates were then compared with analogous estimates of \( S \) and \( \beta \)-cell function obtained from the breakfast meal. The role of potentiation in enhancing \( \beta \)-cell secretion throughout the day was evaluated by comparing the secretion indexes obtained from breakfast with those obtained from lunch and dinner.

RESEARCH DESIGN AND METHODS

Seventeen subjects (14 men, 3 women, aged \( 50 \pm 2 \) years [mean \( \pm \) SE], BMI 25.0 \( \pm \) 0.7 kg/m\(^2\)) were admitted to the University of California at Los Angeles (UCLA) General Clinical Research Center for 6 days. Fasting glucose ranged from 3.6 to 6.6 mmol/l (averaged 5.0 \( \pm \) 0.16 mmol/l); one subject had impaired fasting glucose under the recently revised American Diabetes Association criteria (17), with the remaining subjects having normal fasting glucose (<5.6 mmol/l). Subjects were kept on a weight-maintaining diet and underwent an insulin-modified IVGTT on day 2, an HGC on day 3, and a 24-h glucose, insulin, and C-peptide profile on day 5. The UCLA Institutional Review Board approved the protocol, and all subjects gave written informed consent.

The insulin-modified IVGTT was performed as previously described (13). After a 12-h overnight fast, an intravenous line was inserted in an arm vein for glucose (0.3 g/kg; 50\% solution, time \( = 0 \) min) and insulin (0.03 units/kg bolus, regular insulin, time \( = 20 \) min) administration. A second intravenous line was inserted in a vein in the contralateral arm for drawing blood. Samples were collected at \(-15, 10, 5, -1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, \) and 180 min for measuring plasma glucose and insulin concentrations.

The HGC was performed as previously described (14). After a 12-h overnight fast, an intravenous line was inserted in an antecubital vein for administration of glucose. A second catheter was placed retrograde in a dorsal vein of the contralateral hand for blood withdrawal, and the hand was placed in a heating pad to arterialized the blood. Glucose (50\% solution, 0.15 g/kg) was given at time 0, and a variable glucose infusion (20\%) was subsequently started to maintain plasma glucose at \(-10 \) mmol/l for 180 min. Blood samples were collected at \(-20, 10, 5, 1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, \) and 180 min for measuring plasma glucose, insulin, and C-peptide concentrations.

The 24-h glucose, insulin, and C-peptide profiles were obtained after a 12-h
fast by sampling blood every 20 min between 8:00 A.M. and 10:00 P.M. and every hour until 8:00 A.M. the subsequent morning. Breakfast was served at 8:00 A.M., lunch at 1:00 P.M., and dinner at 7:00 P.M.; no food was allowed between meals except water. Total caloric intake (weight-maintaining diet), percentage of calories by meal (25, 35, and 40% for breakfast, lunch, and dinner, respectively), and carbohydrate content of each meal were recorded for each subject. Biochemical analysis. Plasma glucose concentration was measured by the glucose oxidase method with a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin and C-peptide concentrations were determined by radioimmunoassay with reagents from Linco Research (St. Louis, MO).

Insulin sensitivity analysis from the IVGTT. $S_{\text{IVGTT}}$ was estimated from minimal model analysis (18), in which the minimal model was characterized as:

$$G(t) = -\left[p_1 + X(t)\right] G(t) + p_2 G(t) + R(t) V^{-1}; \quad G(0) = G_0$$

Here, plasma glucose $[G(t)]$ is described with an explicit function for the “rate of glucose appearance” $[R(t)]$. This term was included for consistency with the meal and clamp indexes developed below; for the IVGTT, $R(t)$ is a bolus at time $t = 0$ leading to $G(0) = G_0$ and $G(t)$ is the time immediately following the glucose injection, $G_0$, is the glucose concentration immediately before the glucose injection, $D$ is the dose of glucose injected (0.5 g/kg), and $V$ is the glucose distribution volume (dl/kg). Glucose effectiveness is given by $p_1$ (min$^{-1}$) and insulin sensitivity as $S = V p_2 / (dl \cdot kg \cdot min^{-1} \cdot pmol^{-1})$ expressed in units of clearance per kg body wt).

Insulin sensitivity analysis from the meal tolerance test. $S_{\text{MEAL}}$ was calculated using the glucose and insulin responses during breakfast (interval between 8:00 A.M. and 10:00 P.M). Following Caumo et al. (1), $R(t)$ was assumed to be proportional to the increment in glucose above basal ($G$) and to the rate of change of the increment above basal ($G$). This leads to:

$$S_{\text{MEAL}} = \frac{D_{\text{meal}}}{\text{AUC}[G(t)] - GE} \frac{\text{AUC}[(\Delta G(t)/G(t))]}{\text{AUC}[\Delta I(t)]}$$

Here, $D_{\text{meal}}$ is the amount of glucose ingested during the meal (mg/kg), $f$ is the fraction of the meal that appears in the systemic circulation, and $GE$ is glucose effectiveness in $dl \cdot min^{-1} \cdot kg^{-1}$.

Insulin sensitivity analysis from the HGC. $S_{\text{HGC}}$ was calculated from the plasma glucose concentration ($G_a$), glucose infusion rate ($G_i$) (mg · kg$^{-1}$ · min$^{-1}$), and incremental insulin response ($\Delta G_p$) during steady state (last 30 min of clamp period). Under hyperglycemic clamp conditions, endogenous glucose production is expected to be completely suppressed in nondiabetic individuals (glucose uptake, $G_u$). The glucose uptake rate was assumed to consist of insulin- and non-insulin-mediated components. The non-insulin-mediated component (i.e., the component due to the increase in plasma glucose) was taken as $GE \times \Delta G_a$, where $GE$ was the same value used to derive $S_{\text{MEAL}}$ (0.024 dl/min per kg). The insulin-mediated component (total uptake − glucose-mediated uptake) was normalized to the increment in plasma insulin ($\Delta I$) and the steady-state glucose level ($G_a$):

$$S_{\text{HGC}} = \frac{GE \times \Delta G_a}{G_a \times \Delta I} = \frac{S_{\text{MEAL}}}{G_a \times \Delta I} \frac{G_a \times \Delta I}{G_a \times \Delta I}$$

Normalization to $G_a$ assumes glucose uptake to be proportional to the ambient glucose concentration (19). Equation 3 can also be derived from the steady-state solution of Eq. 1, with $R(t) = G_a - G_d(t) + p_2 V^{-1}$.

Insulin secretion analysis from the IVGTT. First-phase insulin release $[\Phi_{\text{IVGTT}}]$ was estimated as the incremental area under the insulin curve for the 10-min interval following the glucose bolus. Second-phase insulin release could not be estimated from the IVGTT due to the exogenous insulin injection at 20 min.

Insulin secretion analysis from the meal tolerance test. Insulin secretion indexes were calculated using the model proposed by Breda et al. (23). For this model, the secretion response $[S_{R(t)}]$ is characterized by static and “dynamic” components $[S_{R(t)} = S_{R(t)}(t) + S_{R(t)}(t)]$. The static response is delayed with respect to changes in plasma glucose, and the dynamic response $[S_{R(t)}]$ reacts to the rate of increase in glucose but not to its rate of fall:

$$S_{R(t)} = S_{R(t)} + S_{R(t)}(t)$$

where

$$\frac{dS_{R(t)}}{dt} = -\alpha[S_{R(t)} + \gamma(G(t) - h_i)]$$

$$S_{R(t)} = \begin{cases} K_i G(t) & \text{if } dG(t)/dt > 0 \\ 0 & \text{if } dG(t)/dt \leq 0 \end{cases}$$

Here, $\alpha$ is the delay in the static response, $\gamma$ determines the magnitude of the static response (nmol/min per pmol/L), $K_i$ determines the secretory response to the rate of change in plasma glucose (nmol/min per pmol/L), and $h_i$ (pmol/L) is the threshold for glucose-induced insulin secretion (basal insulin secretion $[S_{R(t)}]$ is uniquely determined by the model parameters and the basal C-peptide level). Parameters $\gamma$ and $K_i$ provide static ($\Phi_d$) and dynamic ($\Phi_s$) indexes of β-cell function. Equation 4 assumes glucose levels to be below the threshold for maximal glucose-stimulated insulin secretion (2). Model parameters were identified from the C-peptide response using nonlinear least squares. To this end, the two-compartment C-peptide model proposed by Eaton et al. (20) was used, with kinetic parameters determined according to Van Cauter et al. (21).

Comparison of meal-derived secretion indexes with those obtained with the HGC and IVGTT were performed using the breakfast meal (8:00 A.M. to noon) so as to obtain all estimates under similar fasting conditions (12-h fast). Secretion indexes for the remaining meals were evaluated separately in the intervals noon to 6:00 P.M. (lunch), 6:00 P.M. to midnight (dinner), and midnight to 8:00 A.M. (nighttime), with the identifications performed sequentially (final values from each interval used as the initial conditions for the subsequent interval).

Insulin secretion analysis from the HGC. First-phase insulin release from the HGC $[\Phi_{\text{HGC}}]$ was calculated as the incremental area under the insulin curve for 10 min following the initial glucose bolus. Second-phase insulin release $[\Phi_{\text{HGC}}]$ was calculated as the incremental change in plasma insulin divided by the incremental change in glucose during steady state. Analogous first- and second-phase indexes were obtained from Eq. 4 to allow for direct comparison of model indexes between the meal and clamp.

Statistical analysis. Data are expressed as mean ± SE, except for residuals, for which the mean and 95% CI were used. Model parameters and fractional SDs (FSDs) were obtained using nonlinear least-squares routines (Mlab, Civilized Software, Bethesda, MD). Statistical tests (correlation, runs tests, and repeated-measures ANOVA) were performed with routines available in GraphPad Prism (GraphPad Software, San Diego CA). Dunnett’s test was used for multiple comparisons following the repeated-measures ANOVA, with either the meal-derived indexes (versus IVGTT and HGC) or the breakfast excursion (versus lunch and dinner) as the reference group. Nonparametric statistics were used when evaluating differences in delay time as the parameter was constrained to be positive (causal) and thus does not follow a normal distribution. Median FSD values are reported except where noted.

RESULTS

Insulin sensitivity measures. Figure 1 shows changes in plasma glucose and insulin during the IVGTT, HGC, and breakfast meal. Insulin sensitivity estimated from the meal $[S_{\text{MEAL}} = 2.2 \pm 0.39 \times 10^{-4} \text{ dl/kg min}^{-1} \cdot \text{pmol}^{-1}]$ was $\sim 2.3$ times higher than $S_{\text{IVGTT}}$ (0.96 ± 0.17) and 1.4 times higher than $S_{\text{HGC}}$ (1.6 ± 0.28; $P < 0.05$ for both). $S_{\text{MEAL}}$ was significantly correlated with $S_{\text{IVGTT}}$ ($r = 0.59$; $P < 0.05$ (Fig. 2A), and both $S_{\text{IVGTT}}$ and $S_{\text{MEAL}}$ were correlated with $S_{\text{HGC}}$ ($r = 0.72$ and 0.76, respectively, $P < 0.01$ for each) (Fig. 2B).

Insulin secretion indexes. The breakfast meal was well fit by the insulin secretion model (Fig. 3), but the HGC data had a minor residual run in the early portion of the test (runs test, $P < 0.05$). Although no significant runs were observed with the meal, the delay (1/α) was estimated with a high FSD (mean 115 ± 21.5%, median 74.0%) (Table...
1). $\Phi_1$ and $\Phi_4$ were higher when estimated from the meal than the HGC ($\sim 1.8$ and $3.6$ times, respectively), and the threshold ($h$) was $\sim 15\%$ lower ($P < 0.05$ for all). The delay in the static response tended to be shorter when estimated from the meal compared with the clamp ($P = 0.12$, Wilcoxon matched pairs); however, the response time was not well identified from the breakfast meal in 7 of the 17 subjects (FSD $>100\%$). In five of these cases, the delay time was $<5$ min, suggesting that insulin was being secreted in direct proportion to plasma glucose. Conversely, the delay was well estimated in all subjects during the HGC (mean FSD $23.3 \pm 3.0\%$, median 17.7).

First-phase insulin secretion from the HGC and IVGTT were correlated ($r = 0.96; P < 0.0001$), but neither $\Phi_1^{(\text{HGC})}$ nor $\Phi_1^{(\text{IVGTT})}$ was correlated with $\Phi_1^{(\text{MEAL})}$, and $\Phi_4^{(\text{MEAL})}$ was not correlated with $\Phi_4^{(\text{HGC})}$ (Fig. 4). In contrast, a significant correlation was observed between the static index estimated from the meal ($\Phi_5^{(\text{MEAL})}$) and the clamp second-phase response ($r = 0.69, P = 0.002$), and the model-derived meal and clamp static indexes were correlated ($r = 0.62; P = 0.005$) (Fig. 5).

To assess the diurnal variation in the $\beta$-cell response to meals, secretion indexes were separately assessed during breakfast, lunch, and dinner. This produced good agreement between model fit and data (no significant runs, $P > 0.05$) (data not shown) and indicated that the static index was significantly higher during breakfast compared with lunch or dinner ($P < 0.01$ for both) (Fig. 6A). Differences

![FIG. 1. Plasma glucose (top panels) and insulin (bottom panels) obtained during an IVGTT (A and B), HGC (C and D), and breakfast meal (E and F).](image)

![FIG. 2. A: Insulin sensitivity estimated from the minimal model versus sensitivity estimated from the breakfast meal response. B: Insulin sensitivity estimated from the clamp versus sensitivity estimated from the IVGTT (●) and meal (○).](image)
in the delay time were observed among the three meals (P < 0.05, Friedman’s test) (Fig. 6B), but no pair was significantly different by post hoc analysis. However, the delay time was often estimated with high FSD (median 74, 88, and 127% for breakfast, lunch, and dinner, respectively). Among meals, no differences were observed in either the dynamic index or the threshold for insulin secretion (P > 0.05 for both).

DISCUSSION

That $S_{i(MEAL)}$ was significantly correlated with $S_{i(IVGTT)}$ ($r = 0.59 ; P < 0.05$), but more than two times higher (2.23 ± 0.39 vs. 0.96 ± 0.17 dl/min per mmol/l) (Fig. 2A) is in agreement with an earlier report by Caumo et al. (1), who reported a correlation of 0.89, with $S_{i(MEAL)}$ −2.2 times higher. We extend this observation by demonstrating that $S_{i(MEAL)}$ is also significantly correlated with $S_{i(HGC)}$ ($r = 0.76 , P = 0.0004$), but 1.4 times higher. The fact that both $S_{i(MEAL)}$ and $S_{i(HGC)}$ were higher than $S_{i(IVGTT)}$ suggests that the portal release of insulin during the meal or HGC contributed to the higher estimate of insulin sensitivity. This is in agreement with our study showing that the tolbutamide-modified IVGTT gives higher estimates of insulin sensitivity than the insulin-modified test (13). Nonetheless, a portal insulin effect cannot explain the higher insulin sensitivity estimated from the meal versus the clamp (~40%, 2.23 ± 0.39 vs. 1.60 ± 0.28 dl/kg · min⁻¹ per pmol/l; P < 0.05). Factors that might explain this difference include an inadequate description of the endogenous rate of glucose appearance used in the estimation of $S_{i(MEAL)}$ or an error in the assumed values of glucose effectiveness (0.024 dl/min per kg) and fraction of meal carbohydrate that appears in the blood (80% both obtained from ref. 1).

Although $S_{i(MEAL)}$ and $S_{i(IVGTT)}$ were not equivalent, the two estimates were well correlated ($r = 0.59$) (Fig. 2A). The meal-derived estimate may therefore be considered for assessing insulin sensitivity in epidemiologic and clinical studies since it is easier to perform and more physiologic than the IVGTT. To this end, the performance of the test will need to be evaluated in subjects with impaired glucose tolerance and type 2 diabetes. An estimate of the day-to-day variability will also need to be established in order to determine appropriate study sample sizes (power calculations).

As to the assessment of β-cell function, the meal-derived static index of insulin secretion was correlated with the estimate of second-phase insulin release from the HGC ($r = 0.69$) (Fig. 5A). However, no correlation was observed between the dynamic sensitivity index [K$_i$(MEAL)] and first-phase secretion during the IVGTT or HGC (Fig. 4). This was not due to day-to-day variance in insulin secretion as the HGC and IVGTT first-phase responses were well correlated. Rather, the lack of correlation can likely be attributed to one of three possibilities. The first being that the first-phase component of insulin secretion observed during intravenous glucose challenges is not present during an oral glucose challenge. This is unlikely insofar as K$_i$(MEAL) was well estimated during meals (average FSD 55.9%, median 36.9). The ability to identify this parameter with a CI that excludes zero strongly

### TABLE 1

Parameter estimates from the insulin secretion model (Eq. 4) fit to C-peptide kinetics during the morning meal and HGC (Fig. 4)

<table>
<thead>
<tr>
<th>Test</th>
<th>1/α*</th>
<th>Static index (γ)†</th>
<th>Dynamic index (K$_i$)‡</th>
<th>Threshold (k)$§$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meal</td>
<td>23.2 ± 6.0</td>
<td>0.3070 ± 0.0297</td>
<td>6.01 ± 0.735</td>
<td>4.6 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>(115 ± 21.5)</td>
<td>(32.4 ± 8.5)</td>
<td>(55.9 ± 11.46)</td>
<td>(8.4 ± 1.7)</td>
</tr>
<tr>
<td>HGC</td>
<td>44.7 ± 8.9</td>
<td>0.171 ± 0.0153</td>
<td>1.69 ± 0.213</td>
<td>5.4 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>(23.3 ± 3.0)</td>
<td>(33.2 ± 4.7)</td>
<td>(10.7 ± 1.6)</td>
<td>(31.1 ± 17.1)</td>
</tr>
</tbody>
</table>

Data are means ± SE. FSDs are shown in parentheses (see text for median values). One meal response in which 1/α approached 0 was excluded because both 1/α and its FSD are infinite at α = 0. Units on γ and K$_i$ assume that glucose is measured in millimoles per liter and secretion is predicted in nanomoles per minute. Units of measurement: *minutes; †nmol · min⁻¹ per mmol/l; ‡nmol · min⁻¹ per mmol/l · min⁻¹; §nmol/l.
suggests that a rate-of-change component is present during meals.

The second possibility is that the model used to fit the meal C-peptide response was inappropriate. Equation 4 represents only one of several models for assessment of β-cell function (2–10). The models are all similar insofar as each describes glucose-induced insulin secretion in terms of components that react immediately to changes in glu-

FIG. 4. A: Correlation of first-phase insulin release estimated from the IVGTT versus first-phase insulin release estimated from the HGC. B: Correlation of first-phase insulin release estimated from the IVGTT with the dynamic secretion index estimated from the breakfast meal. C: Correlation of the HGC first-phase response with the dynamic secretion index estimated from the breakfast meal. D: Correlation of the dynamic secretion index estimated from the clamp with the same index estimated from the breakfast meal.

FIG. 5. A: The relation between second-phase insulin release estimated from the HGC and the static secretion index estimated from the meal. B: The relation between the static secretion index estimated from the HGC with the same index estimated from the meal.
cose, have a delayed reaction, and/or react to the rate-of-change of glucose. The model of Eq. 4 has the delayed and rate-of-change components and was chosen based on the similarity of its theoretical response to a step increase in glucose and the response traditionally observed during an HGC (14). Of the remaining models, the one proposed by Mari and colleagues (4–6) has the same rate-of-change component as Eq. 4 but does not include a delay in the static response (i.e., has the clamp-like, first-phase response but no rise in second phase). The model proposed by Cretti et al. (7) has a delayed component but no immediate or rate-of-change component (no clamp-like, first-phase response). The model proposed by Hovorka et al. (8) has an immediate but no delayed or rate-of-change component (no first-phase response and no rise in second phase). The model proposed by Cerasi et al. (9,10) has a proportional component similar to the model proposed by Mari and colleagues (4–6), but does not have an explicit “rate-of-change” term. This last model is nonetheless interesting in that it does have a theoretical biphasic clamp response resulting from the difference in time-dependent potentiation and inhibition factors.

While a complete assessment of all the models (2–10) is beyond the scope of the present work, several observations can be made from the present data. First, the model used here was able to fit both the meal and HGC response, with only minor residuals during the clamp (Fig. 4). The response time (1/$\alpha$) was, however, often estimated with inappropriately high FSDs. This was predominately due to subjects in whom no delay was observed during the meal (5 of the 17 breakfast responses had 1/$\alpha$ < 5 min). The existence of the delay term has not previously been established for meals, although it has been shown (3) to be essential when describing insulin secretion during a graded glucose infusion. The model proposed by Mari et al. (5), which does not have a delay in the static response, has been successfully applied to meal data obtained over 24 h and is consistent with our results, showing 1/$\alpha$ to be <5 min in 5 of the 17 subjects. Nonetheless, the observation that the delay was well estimated in the remaining 12 subjects supports arguments for its existence (2,3,22,23), and significant differences in this parameter were observed during the course of the day (Fig. 6B). The inability to resolve whether the meal response has a consistent delay in its static response suggests that the $\beta$-cell may have a rate-of-change component together with both an immediate and delayed response to glucose, with the delayed response suppressed in some cases via diurnal variation or other metabolic factors. Further work is needed to explore these possibilities and to evaluate the Cerasi model (9,10) under meal conditions.

The third possibility for the lack of correlation between $K_{D,\text{MEAL}}$ and first-phase insulin release during an HGC or IVGTT is that meal-specific factors dramatically alter the response. These factors include incretin effects (24), various neural signals (25), and the presence of free fatty acids (FFAs) and other secretagogues in the meal. However, to the extent that these factors “potentiate” glucose-induced insulin secretion rather than directly stimulate it, the underlying model structure would remain intact, with only the estimated parameter values affected. This could explain the observation that the insulin response is well described under both meal and clamp conditions in the absence of a significant correlation in the dynamic components. Incretins may also explain the faster response times observed during oral compared with intravenous glucose (23.6 ± 6.0 vs. 45.4 ± 8.4 min).

The observation that the increase in the static and dynamic components was different for oral versus intravenous glucose suggests that the components are independently regulated (the static index increased 1.8 times, whereas the dynamic index increased 3.6 times). Generally, factors that are mediated by gut hormones appear to potentiate both first and second phase equally when glucose is the only stimulus. Shapiro et al. (26) showed that the insulin response during an oral glucose tolerance test was ~44% higher than the response obtained with glucose infused intravenously at a rate to match the oral glucose tolerance test plasma glucose level. In that study, the shape of the C-peptide responses were virtually superposable, suggesting that first and second phase were equally potentiated. An HGC study performed with and without preingestion of oral fat also concluded that first- and second-phase insulin release were equally potentiated (~2-fold) (14), although a similar clamp study, in which the FFA level was elevated with an intravenous infusion of intralipid/heparin, showed that only the second phase was potentiated (17–25%) (27). Finally, a study comparing meal-induced insulin secretion with and without a concomitant intravenous glucagon-like peptide-1 infusion concluded that insulin secretion is augmented by glucagon-like peptide-1 in the absence of potentiation of the rate-of-change component ($K_p$) (28).

Despite incomplete resolution of all of the modeling issues, our data, and those of others (2–7), show that the
meal response is well described by a multiphase insulin secretion model involving, at a minimum, a dynamic component and a proportional component with or without delay. In light of this, we characterized the β-cell secretory response over the course of a complete day. To account for intraday potentiation, the model parameters were allowed to assume different values during breakfast, lunch, dinner, and overnight. This approximation to the diurnal variation in insulin secretion resulted in good agreement with the data and indicated a significant enhancement in the static response at breakfast (Fig. 6A) compared with lunch or dinner. No changes were observed in the dynamic component. These observations support the underlying potentiation structure proposed by Mari et al. (5) wherein the static, but not the dynamic, component is affected by diurnal variation.

In conclusion, the present study showed that indexes of insulin sensitivity and β-cell function could both be obtained from a meal test. The indexes were not, however, equivalent to analogous estimates obtained from an HGC or IVGTT. The meal-derived insulin sensitivity index correlated with insulin sensitivity estimated from the IVGTT and HGC, but was significantly higher. However, as the meal test is easier to perform, the index may still be preferable for epidemiologic or clinical studies designed to assess changes in insulin sensitivity. To this end, the interdaily variance in the meal estimate will need to be determined before appropriate sample size calculations can be performed. As to the assessment of β-cell function, the meal-derived estimate of the β-cell’s static index was correlated with the HGC second-phase response, but the dynamic index did not correlate with the first-phase insulin response calculated from either the IVGTT or HGC. This raises questions as to validity and applicability of the model-derived indexes. Until the differences in various β-cell models can be resolved, care will need to be taken in comparing model results to those obtained with traditional tests such as the HGC or IVGTT. Finally, the performance of the insulin sensitivity and secretion indexes will need to be evaluated in subjects with impaired glucose tolerance or type 2 diabetes.

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