Original Article

Two-Hour Seven-Sample Oral Glucose Tolerance Test and Meal Protocol

Minimal Model Assessment of β-Cell Responsivity and Insulin Sensitivity in Nondiabetic Individuals

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Highly informative yet simple protocols to assess insulin secretion and action would considerably enhance the quality of epidemiological and large-scale clinical trials. In an effort to develop such protocols, a 5-h, 11-sample oral glucose tolerance test (OGTT) was performed in 100 individuals and a 7-h, 21-sample meal in another 100. Plasma glucose, insulin, and C-peptide concentrations were measured. We show that virtually the same minimal model assessment of β-cell responsivity (dynamic [Φ_d] and static [Φ_s]), insulin sensitivity (S_i), and disposition index (DI) can be obtained with a reduced seven-sample 2-h protocol: Φ_d, reduced versus full: 871.50 vs. 873.32, $r = 0.98$ in OGTT and 494.88 vs. 477.99 10^{-9}, $r = 0.91$ in meal; Φ_s: 42.36 vs. 44.35, $r = 0.88$ in OGTT and 35.31 vs. 35.37 10^{-9} min^{-1}, $r = 0.90$ in meal; S_i: 24.33 vs. 22.77 10^{-5} $dl \cdot kg^{-1} \cdot min^{-1}$ per pmol/l, $r = 0.89$ in OGTT and 19.03 vs. 19.77 10^{-5} $dl \cdot kg^{-1} \cdot min^{-1}$ per pmol/l, $r = 0.85$ in meal; and DI: 1,282.26 vs. 1,273.23, $r = 0.84$ in OGTT and 726.92 vs. 776.97 10^{-14} $dl \cdot kg^{-1} \cdot min^{-2}$ per pmol/l, $r = 0.84$ in meal. This reduced protocol will facilitate the study of insulin secretion and action under physiological conditions in nondiabetic humans. *Diabetes* 54:3265–3273, 2005

The oral meal or oral glucose tolerance test (OGTT) glucose and C-peptide minimal models can simultaneously measure insulin action, β-cell function, and the rate of meal glucose appearance (1–5). These models have been subjected to various validation strategies, including multiple tracer protocols (6) and euglycemic and hyperglycemic clamp studies (7,8) and have been used in pathophysiological studies (9). All of the above studies have relied on a 300-min OGTT and 420-min meal protocols in which plasma glucose, insulin, and C-peptide concentrations have been sampled 11 and 21 times, respectively (Fig. 1*A*). Since this large number of samples and prolonged period of study is not feasible for large population-based studies, we sought to determine whether a seven-sample protocol performed over 120 min could provide estimates of insulin secretion and action equivalent to those obtained with the longer and more complex studies. To do this, we analyzed data from 200 studies consisting of 100 5-h, 11-sample OGTTs and 100 7-h, 21-sample meal studies performed in subjects with various degrees of glucose tolerance. We report that a seven-sample protocol performed over 120 min following ingestion of either a mixed meal or 75 g glucose enables accurate assessment of both insulin secretion and action in nondiabetic humans.

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AUC, area under the curve; DI, disposition index; OGTT, oral glucose tolerance test.

RESEARCH DESIGN AND METHODS

One hundred nondiabetic subjects underwent an OGTT performed at the Division of Endocrinology, Metabolism, and Lipid Research, Washington University School of Medicine, St. Louis, Missouri, and 100 nondiabetic subjects underwent a mixed meal test performed at the Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota. All subjects provided informed consent.

The OGTT consisted of oral administration of 75 g glucose at time 0; as detailed in (2), blood samples were collected at time 0, 10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 min, and plasma glucose, insulin, and C-peptide concentrations were measured. Subject characteristics are reported in Table 1 (*right column*).

The mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein, and 40% fat) contained 1 ± 0.02 g/kg glucose. As detailed in (9), plasma samples were collected at 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, and 420 min, and plasma glucose, insulin, and C-peptide concentrations were measured. Subject characteristics are reported in Table 1 (*left column*).

Oral glucose minimal model. Insulin sensitivity (S_i; $dl \cdot kg^{-1} \cdot min^{-1}$ per pmol/l) was estimated from plasma glucose and insulin concentrations measured during the test by using the oral glucose minimal model (4,6). The model is shown in Fig. 2*A*. S_i measures the overall effect of insulin to stimulate glucose disposal and inhibit glucose production. The model also reconstructs the rate of appearance (R_a; $mg \cdot kg^{-1} \cdot min^{-1}$) in plasma of ingested glucose.

Oral C-peptide minimal model. β-Cell responsivity indexes were estimated from plasma glucose and C-peptide concentrations measured during the test by using the oral C-peptide minimal model (2,3,5). The model is shown in Fig. 2*B*. Insulin secretion is made up of two components. The dynamic component is likely to represent secretion of promptly releasable insulin and is proportional to the rate of increase of glucose concentration through a parameter, Φ_d (10^{-9}), that defines the dynamic responsivity index. The static component derives from provision of new insulin to the releasable pool and is character-

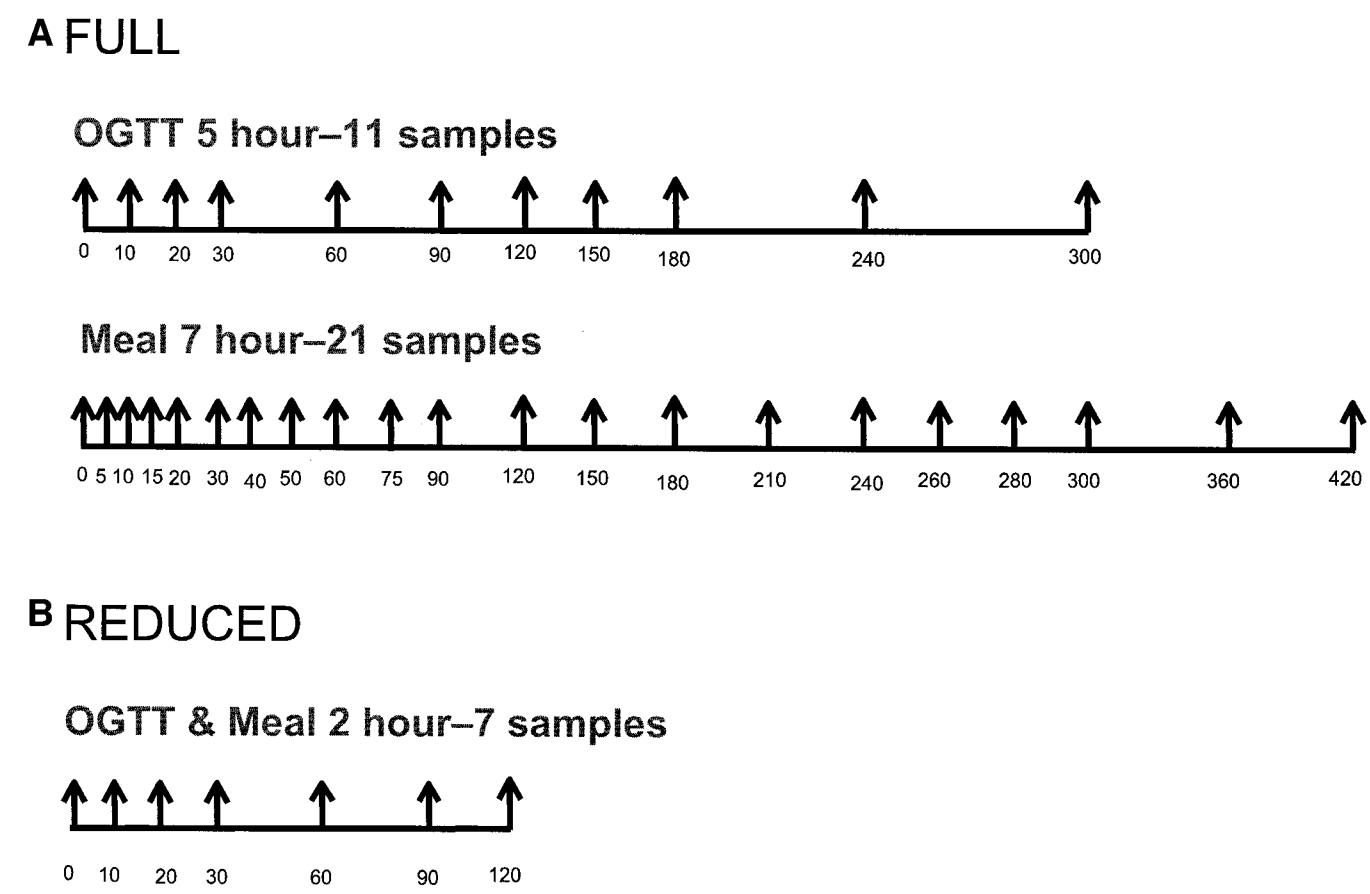

FIG. 1. ***A*: Full protocol sampling schedule of OGTT (5 h, 11 samples) and meal (7 h, 21 samples).** ***B*: Reduced protocol sampling schedule for both OGTT and meal (2–7 h samples).**

ized by a static index, Φ_s (10^{-9} min^{-1}), and by a delay time constant (T; min). The meaning of Φ_s and T can be made clear with reference to a response to an above-basal step increase of glucose: provision tends with time constant T toward a steady state that is linearly related to the glucose step size through parameter Φ_s.

Φ_d and Φ_s can also be expressed in relation to insulin sensitivity through the dynamic (DI_d) and static (DI_s) disposition indexes, i.e., $DI_d = \Phi_d \times S_i$ and $DI_s = \Phi_s \times S_i$. Since from Φ_d and Φ_s one can also calculate a single overall β-cell responsivity, Φ (10^{-9} min^{-1}), a single overall DI can also be derived as $DI = \Phi \times S_i$. The model also reconstructs insulin secretion (SR; pmol/min) and its dynamic (SR_d) and static (SR_s) components.

Model identification. The oral glucose and C-peptide minimal models of Fig. 2 were numerically identified in both full and reduced protocol OGTT and meal studies, as detailed in (2,4,6). Two comments are in order. The first concerns the fraction of ingested glucose that is absorbed (area under the curve [AUC] of R_a from time 0 to 7 h divided by the dose). This value is fixed a priori to 0.90 in the full protocol identification of the glucose minimal model (6). In the reduced protocol identification, it is fixed at the same value by extrapolating R_a from 2 to 7 h with a decay constant of 60 and 125 min (obtained from full protocol studies) in OGTT and meal studies, respectively. The second concerns the glucose threshold above which secretion occurs in the C-peptide minimal model. This was fixed to the basal glucose value instead of estimated, since the 2-h data does not have enough information to allow a reliable estimation of the threshold. This approach introduces no appreciable bias, since the estimated threshold is within a few percent of the basal glucose values (2,5).

Statistical analysis. Data are presented as means ± SE. Two-sample comparisons were done by Wilcoxon signed-rank test (significance level set to 5%). Pearson's correlation was used to evaluate univariate correlation. Bland-Altman plot was used to represent the agreement of the methods.

TABLE 1
Subjects characteristics

	OGTT	MEAL
n	100	100
Basal glucose (mmol/l)	5.08 ± 0.05 (4.31–6.94)	5.10 ± 0.04 (4.25–5.83)
Basal insulin (pmol/l)	47.94 ± 3.54 (12.00–222.60)	25.98 ± 1.26 (9.00–87.00)
Basal C-peptide (pmol/l)	573.76 ± 37.33 (132.40–2,158.12)	469.53 ± 15.01 (110.00–985.00)
Age (years)	34 ± 1 (12–64)	55 ± 2 (19–87)
BMI (kg/m^2)	26.19 ± 0.56 (15.68–48.67)	26.56 ± 0.16 (19.73–35.36)

Data are means ± SE (range of variability).

RESULTS

Plasma concentrations. Average plasma glucose, insulin, and C-peptide concentration in OGTT and meal studies in the basal state are reported in Table 1 together with their SE and range of variability, while their average profiles during OGTT and meal are shown in Fig. 3 (*left* and *right panel*, respectively) together with their range of variability (gray area). Range of variability in overall OGTT and meal studies was at basal 4.31–6.94 mmol/l, 9.00–222.60 pmol/l, and 110–2,158 pmol/l and at peak 6.77–16.26 mmol/l, 132–2,028 pmol/l, and 1,130–6,710 pmol/l for glucose, insulin, and C-peptide concentrations, respectively.

Glucose minimal model: R_a and S_i. The model fit in OGTT and meal studies is shown in Fig. 4*A* and *B*. Model predictions during reduced protocol are almost superimposable on those of the full protocol in OGTT, while in meal one can note small differences that are essentially

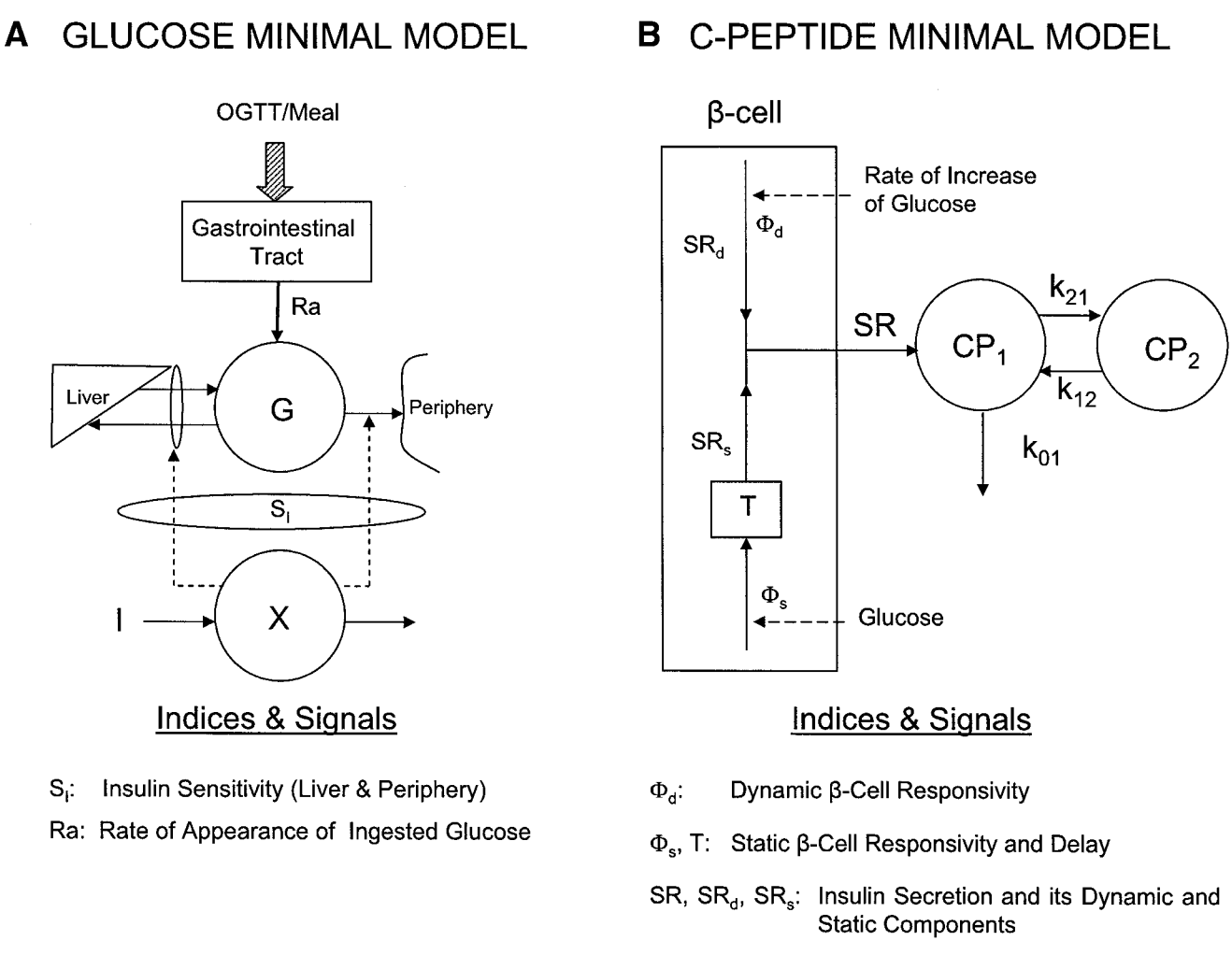

FIG. 2. ***A*: Glucose oral minimal model with its key indexes and signals: insulin sensitivity (S_i) and rate of appearance of ingested glucose (R_a); I, plasma insulin concentration; X, insulin action.** ***B*: C-peptide oral minimal model with its key indexes and signals: dynamic (Φ_d) and static (Φ_s) β-cell responsivity, delay of provision of new insulin (T), and insulin secretion (SR) with its dynamic (SR_d) and static (SR_s) components.**

due to the higher number of samples present in the first 2 h in meal studies.

The average R_a of ingested glucose during OGTT and meal is shown in Fig. 5*A* and *B*. R_a of the reduced protocol well describes the full protocol R_a up to 120 min in both oral tests. S_i estimates are shown in Fig. 6 (*first panel*, *left* and *right*, respectively) for the two tests. The reduced protocol S_i values are not significantly different and well correlated to those obtained with the full protocol: (reduced versus full) 24.33 ± 1.92 vs. 22.77 ± 1.45 10^{-5} dl · kg^{-1} · min^{-1} per pmol/l, $r = 0.89$ in OGTT and 19.03 ± 1.38 vs. 19.77 ± 1.20 10^{-5} dl · kg^{-1} · min^{-1} per pmol/l, $r = 0.85$ in meal. For both tests, the regression line is not different from the identity line (both slopes and zero intercept). The good agreement between the two tests is also evident from Bland-Altman plots, which show that the differences between full and reduced protocol estimates are not related to the size of the measurement (Fig. 6, *right upper panel*). Precision of S_i estimate (expressed as coefficient of variation) was decreased in the reduced protocol with respect to full protocol (18 and 15% vs. 6 and 5% in OGTT and meal, respectively).

C-peptide minimal model: insulin secretion and β-cell responsivity. The model fit in OGTT and meal studies is shown in Fig. 4*C* and *D*. The average insulin secretion (SR) during OGTT and meal is shown in Fig. 5*C* and *D*, where its dynamic (SR_d) and static (SR_s) components of SR are also shown. The reduced and full protocol reconstructed SR, SR_d, and SR_s are virtually superimposable during both OGTT and meal. Dynamic (Φ_d) and static (Φ_s) β-cell responsivity indexes are shown in Fig. 6 for the two tests (*second* and *third panel*). The reduced protocol values of Φ_d and Φ_s are not significantly different and well correlated to those obtained with the full protocol: Φ_d is (reduced versus full) 871.50 ± 45.80 vs. 873.32 ± 47.34 10^{-9}, $r = 0.98$ and 494.88 ± 25.16 vs. 477.99 ± 24.69 10^{-9}, $r = 0.91$ and Φ_s is 42.36 ± 1.57 vs. 44.35 ± 1.87 10^{-9} min^{-1}, $r = 0.88$ and 35.31 ± 1.13 vs. 35.37 ± 1.12 10^{-9} min^{-1}, $r = 0.90$ in OGTT and meal, respectively. The delay constant T is also not significantly different and correlated in the reduced and full protocol: 10.59 ± 0.46 vs. 9.98 ± 0.67 min, $r = 0.60$ and 12.46 ± 0.77 vs. 13.71 ± 0.83 min, $r = 0.54$ in OGTT and meal, respectively. Finally, the single overall β-cell responsivity index Φ is 54.57 ± 2.03 vs. 56.43 ± 2.53 10^{-9} min^{-1}, $r = 0.85$ and 39.74 ± 1.21 vs. 40.02 ± 1.27 10^{-9} min^{-1}, $r = 0.87$ in OGTT and meal, respectively (Fig. 6, *lower panel*). For both tests, the regression line is not different from the identity line (both slopes and zero intercept). Bland-Altman plots show that the differences between full and reduced protocol estimates are not related to the size of the measurement (Fig. 6, *on the right of each panel*). Precision of Φ_d, Φ_s, Φ, and T estimates

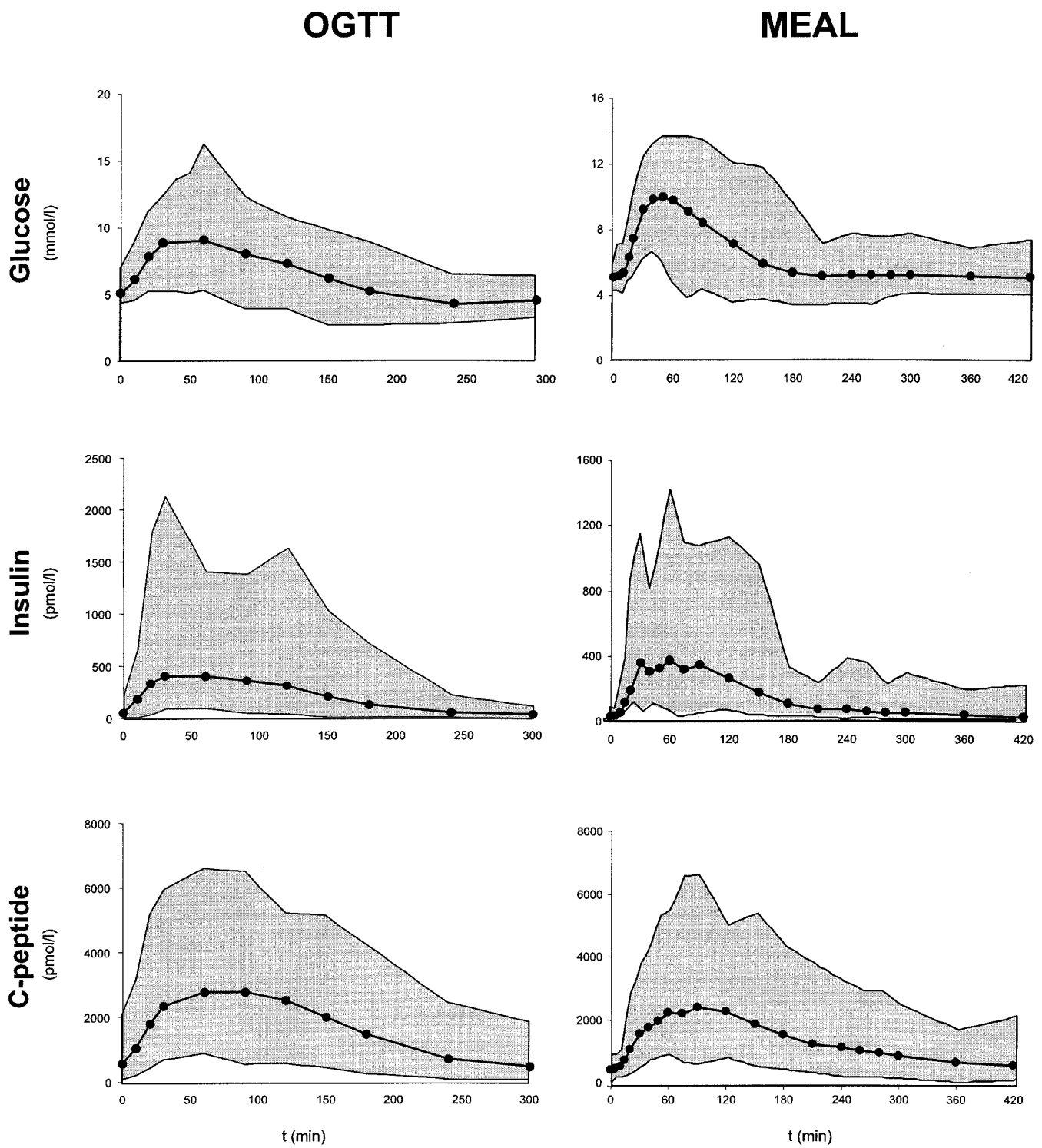

FIG. 3. Average plasma glucose, insulin, and C-peptide concentration during OGTT (*left panel*) and meal (*right panel*). The gray area represents the range of variability.

(expressed as coefficient of variation) in the reduced protocol was similar to that of the full protocol in both OGTT (21 vs. 24%, 11 vs. 15%, 7 vs. 15%, and 43 vs. 40%, respectively) and meal (30 vs. 28%, 10 vs. 9%, 8 vs. 9%, and 41 vs. 31%, respectively).

DI. The reduced and full protocol DIs, DI_d, DI_s, and DI, are shown in Fig. 7. They are not significantly different and well correlated. DI_d is (reduced versus full) 18,477.58 ± 1,432.84 vs. 17,845.13 ± 1,214.89 10^{-14} dl · kg^{-1} · min^{-1} per pmol/l, $r = 0.85$ and 9,363.59 ± 846.94 vs. 9,427.57 ± 757.15 10^{-14} dl · kg^{-1} · min^{-1} per pmol/l, $r = 0.89$; DI_s is 980.12 ± 84.4 vs. 1,010.00 ± 85.06 10^{-14} dl · kg^{-1} · min^{-2} per pmol/l, $r = 0.91$ and 636.17 ± 47.40 vs. 674.26 ± 41.90 10^{-14} dl · kg^{-1} · min^{-2} per pmol/l, $r = 0.84$; and DI is 1,282.26 ± 110.38 vs. 1,273.23 ± 105.49 10^{-14} dl · kg^{-1} · min^{-2} per pmol/l, $r = 0.84$ and 726.92 ± 55.48 vs. 776.97 ± 51.27 10^{-14} dl · kg^{-1} · min^{-2} per pmol/l, $r = 0.84$ in OGTT and meal, respectively. For both tests, regression line is not

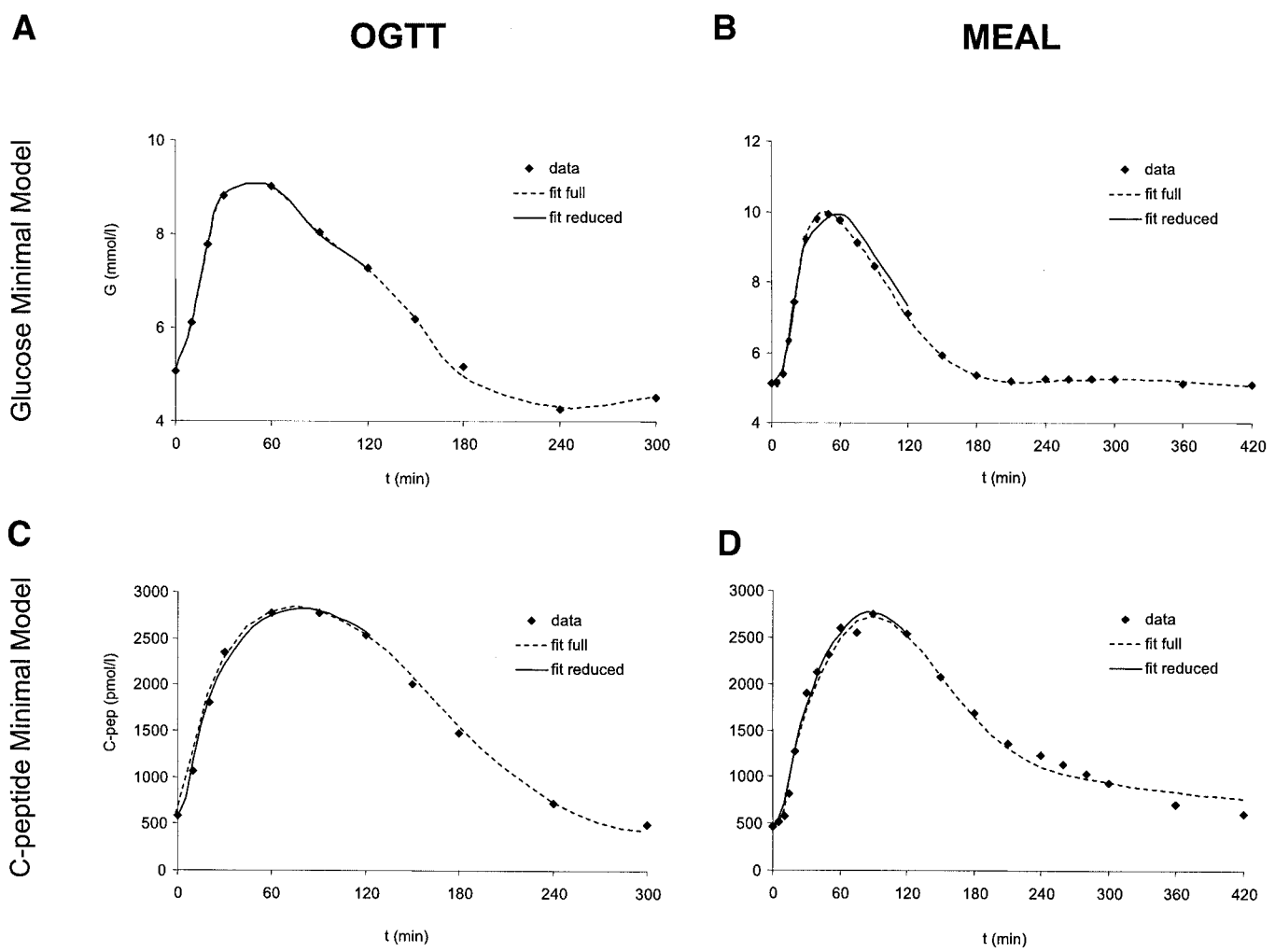

FIG. 4. ***A*** **and** ***B*****: Measured glucose concentration (♦) against glucose minimal model prediction obtained with the full (dashed line) and reduced (solid line) protocol during OGTT (*A*) and meal (*B*). *C* and *D*: Measured C-peptide concentration (♦) against C-peptide minimal model prediction obtained with the full (dashed line) and the reduced (solid line) protocol during OGTT (*C*) and meal (*D*).**

different from the identity line (both slopes and zero intercept). Bland-Altman plots show that the differences between full and reduced protocol estimates are not related to the size of the measurement (Fig. 7, *on the right of each panel*).

DISCUSSION

There is an increasing demand of highly informative yet relatively simple protocols to assess insulin action and β-cell function in epidemiological and large-scale clinical trials. We have focused on the oral glucose route of delivery, i.e., OGTT or meal in nondiabetic individuals with a large spectrum of glucose tolerance (Table 1, Fig. 3). We have shown that indexes of insulin action and β-cell function can be reliably estimated using the glucose and C-peptide oral minimal models by measuring plasma glucose, insulin, and C-peptide concentrations at 0, 10, 20, 30, 60, 90, and 120 min after glucose or meal ingestion and interpreting these measurements.

The oral route of glucose delivery is clearly more physiological than intravenous glucose injection or continuous infusion of insulin during an hyperinsulinemic clamp. However, measuring insulin action following ingestion of glucose or a mixed meal is more difficult than after intravenous glucose injection. This is because the systemic rate of appearance of exogenous glucose following intravenous glucose injection equals the administered dose, whereas it must be estimated with a model of the glucose system following glucose ingestion. In an effort to avoid this limitation, a new oral glucose minimal model that enables measurement of insulin sensitivity has been developed and validated against multitracer (6) and euglycemic-hyperinsulinemic clamp (7) protocols. In addition, use of a C-peptide minimal model (2,5) that has been validated both against hyperglycemic clamp (8) and intravenous glucose tolerance test (9) protocols allows concurrent measurement of insulin secretion. This enables determination of whether β-cell function is appropriate for the prevailing level of insulin action (10,11).

The database used in the present studies consisted of 100 OGTT and 100 meal tolerance tests performed in individuals who had a wide range of glucose tolerance. All 200 individuals underwent what we refer to as a full oral protocol, i.e., a 5-h OGTT with 11 samples or a 7-h meal with 21 samples (2,9). Plasma measurements of glucose, insulin, and C-peptide interpreted with the full glucose and C-peptide oral minimal models provided reference values to which the shortened protocol were compared. As

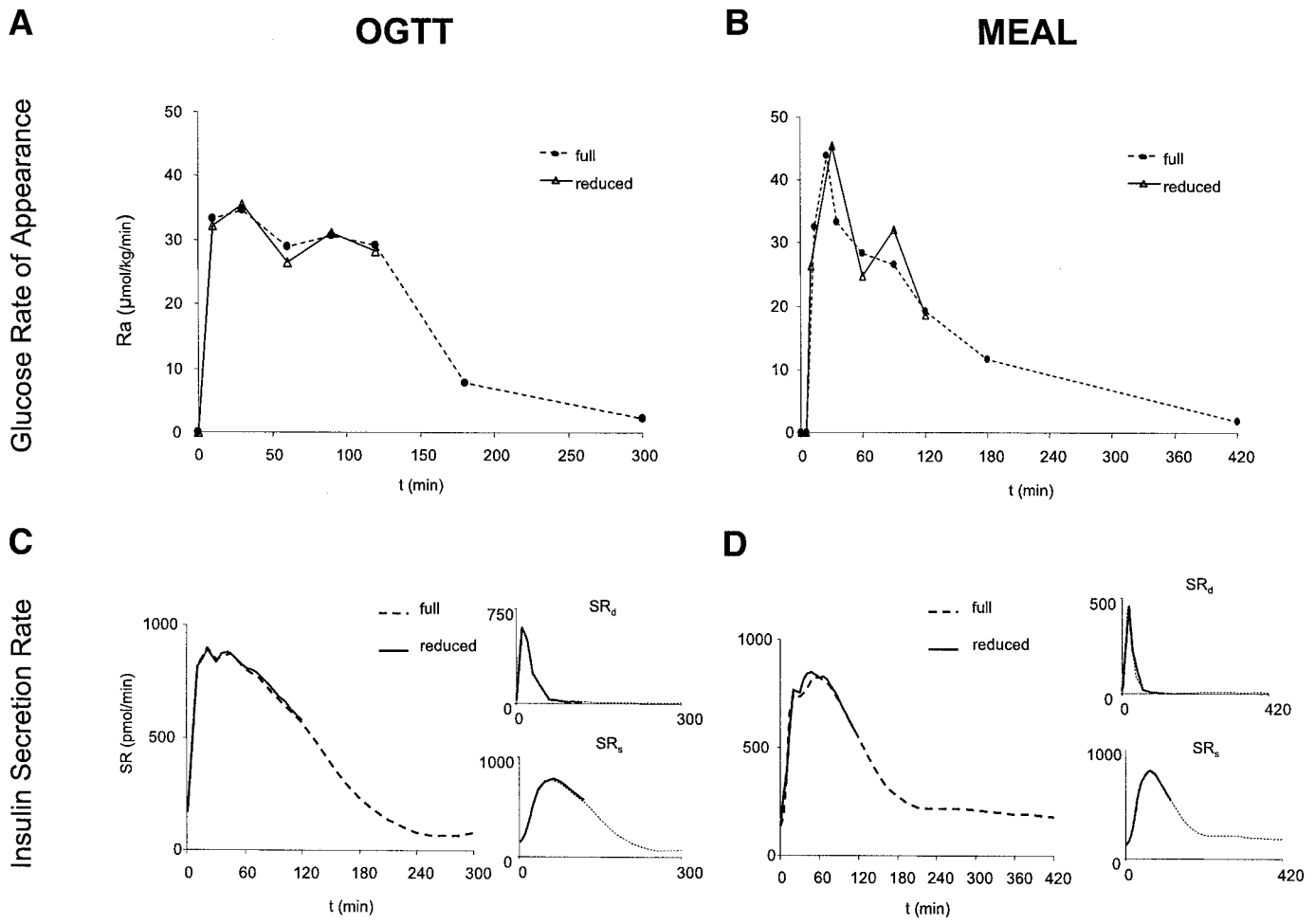

FIG. 5. ***A*** **and** ***B*****: Comparison between the average rate of appearance of ingested glucose, R_a, obtained with the full and the reduced protocol during OGTT (*A*) and meal (*B*).** ***C*** **and** ***D*****: Comparison between the average insulin secretion, SR, and its dynamic (SR_d) and static (SR_s) components obtained with the full and the reduced protocol during OGTT (*C*) and meal (*D*).**

shown in Figs. 5–7, the full and reduced protocol exogenous glucose appearance rates and indexes of insulin secretion and action were highly correlated during both the OGTT and meal.

The proposed 2-h duration of the reduced protocol is the same as that of a standard OGTT. It also retains the typical 0- and 120-min samples with the addition of samples at 10, 20, 30, 60, and 90 min. Of note, the samples at 10 and 20 min are required for an accurate and precise estimation of the dynamic β-cell responsivity, Φ_d, which by definition relies on the data where glucose is increasing. When these sample times are included, the ability of the reduced protocol to reconstruct the secretion indexes obtained during the full protocol is remarkable. As is evident in Fig. 6, Φ, Φ_d, Φ_s, and T, calculated with the reduced protocol, are virtually identical to those calculated with the full protocol. Of interest, the correlation of T was somewhat lower, likely due to lower precision of its estimation during the reduced protocol. Since insulin sesitivity is also highly correlated, the reduced and full protocols yielded virtually identical estimates of the DIs DI, DI_d, and DI_s, thereby enabling assessment as to whether insulin secretion was appropriate for the degree of insulin resistance

We believe the ability to obtain a virtually identical insulin secretion and action portrait by using only the first 2-h portion of a 5-h OGTT or 7-h meal is due to the predictive power inherent in a model of system. In other words, the two oral minimal models, with modest additional knowledge, i.e., the extrapolation of the rate of appearance of ingested glucose, R_a, beyond the 2 h for the glucose model, only need the first 2 h of information to provide an accurate picture in a nondiabetic population. To better appreciate the predictive power of the oral minimal model method, it is of interest to contrast it with an AUC approach. This is possible because, e.g., dynamic (Φ_d) and static (Φ_s) β-cell responsivity indexes are also amenable to an AUC interpretation. It is easy to show (2,5) that Φ_d, besides being a parameter of the C-peptide oral minimal model, also represents the AUC of SR_d per unit increase of glucose concentration; similarly, Φ_s is the AUC of above-basal SR_s per AUC of above-basal glucose concentration. We are thus in the position to compare the reduced with the full protocol AUC values of Φ_d and Φ_s calculated directly from the data. Of interest, when calculated in this manner, AUC Φ_s values of the reduced protocol are in this case significantly higher that those of the full protocol: 50.19 ± 1.97 vs. 44.34 ± 1.87 ($P < 0.0001$) and 39.36 ± 1.29 vs. 35.37 ± 1.12 min^{-1} ($P < 0.0001$) in OGTT and meal, respectively. Also, correlation deteriorated ($r = 0.70$) in both OGTT and meal with respect to C-peptide model Φ_s.

In conclusion, we have shown that seven samples obtained during the first 2 h after ingestion of either 75 g glucose or a mixed meal enables accurate assessment of

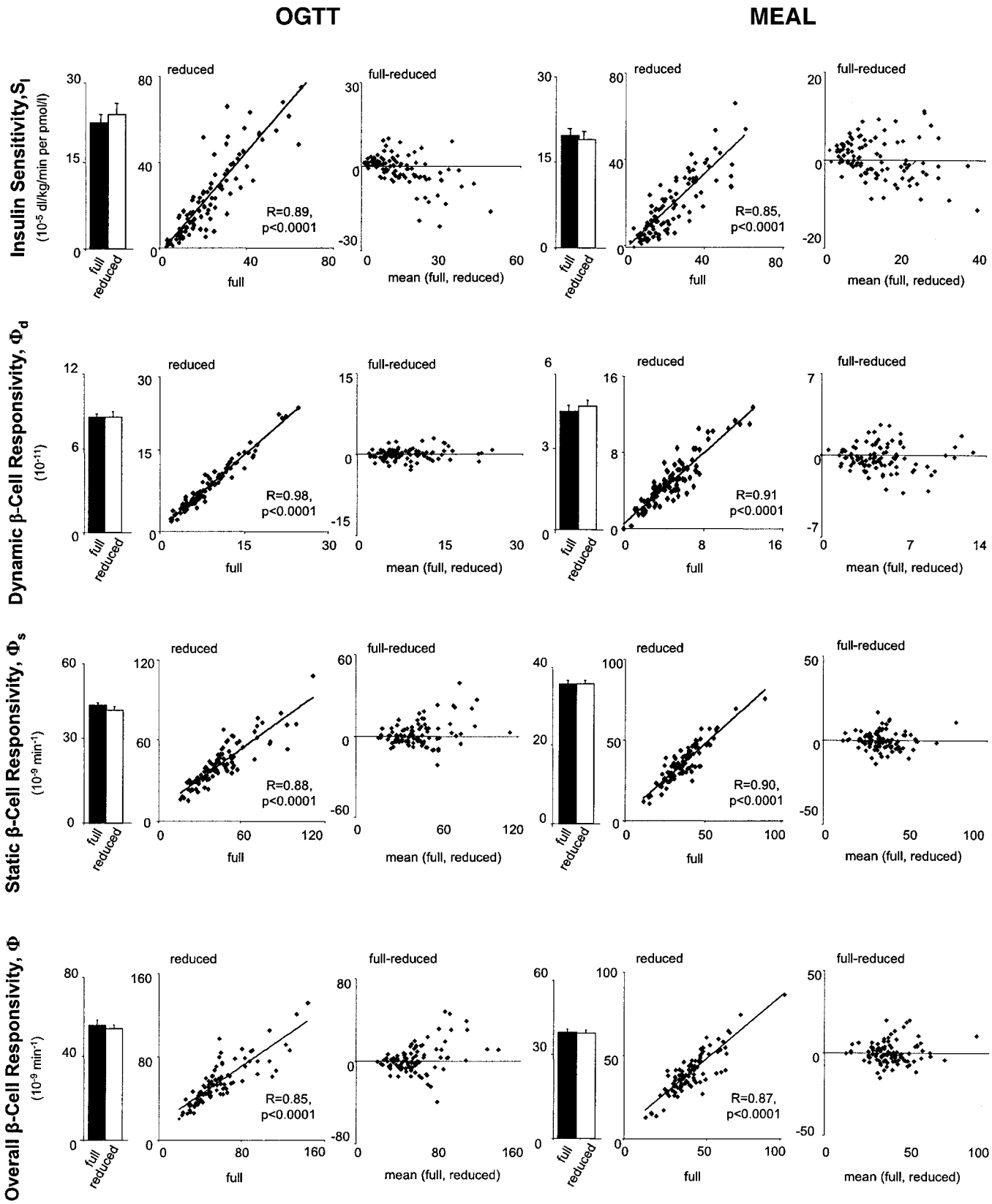

FIG. 6. ***First panel*: Comparison between insulin sensitivity, S_i, obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). *Second panel*: Comparison between dynamic responsivity, Φ_d, obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). *Third panel*: Comparison between static responsivity, Φ_s, obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). *Lower panel*: Comparison between total responsivity, Φ, obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). Means ± SE, correlation plot, and Bland-Altman plot are shown. The line in the correlation plot represents the regression line, which is not statistically different from the identity line.**

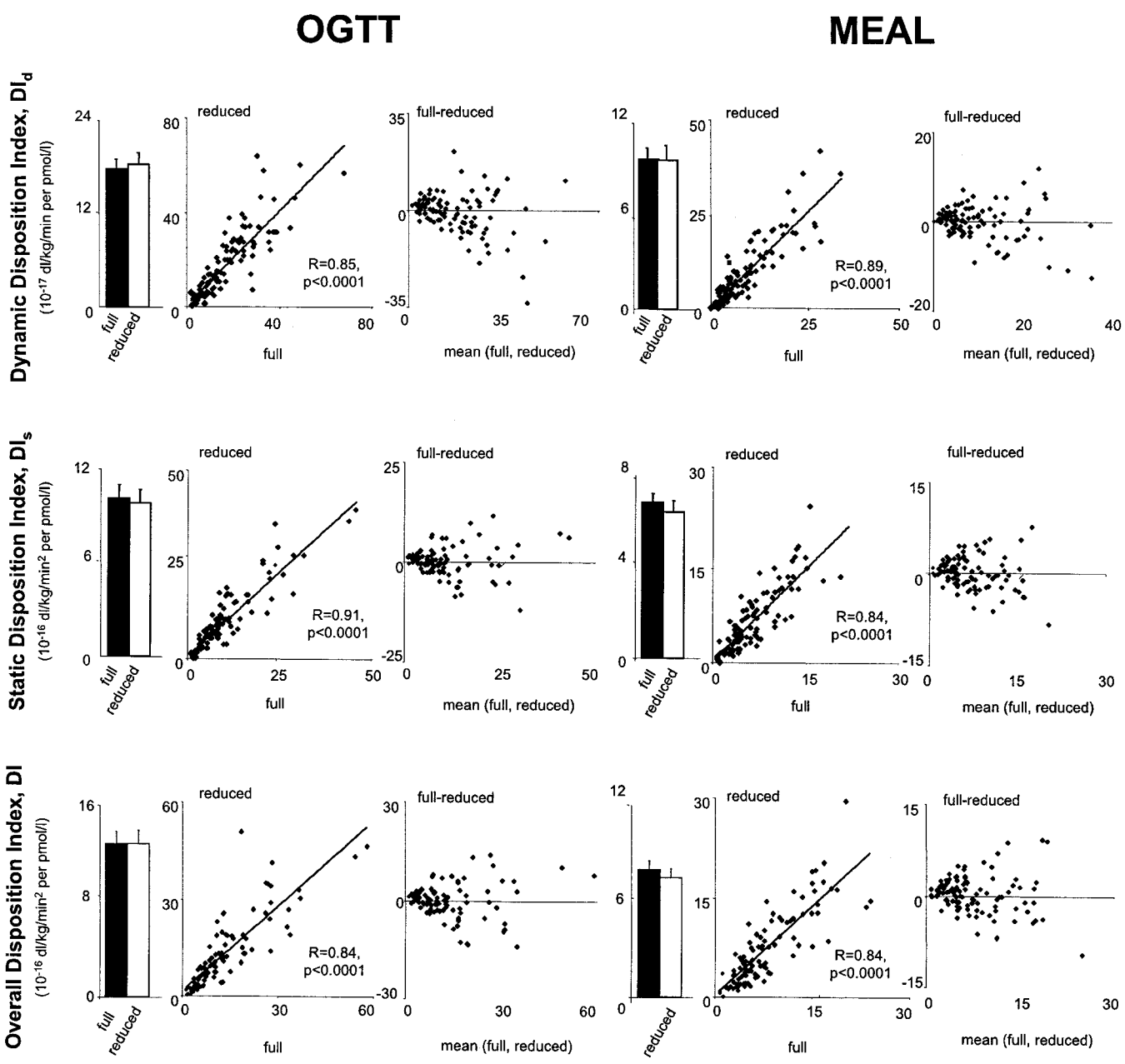

FIG. 7. ***First panel*: Comparison between DI_d (definition of the indexes are reported in section ORAL C-PEPTIDE MINIMAL MODEL) obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). *Middle panel*: Comparison between static DI_s obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). *Lower panel*: Comparison between total disposition index, DI_s, obtained with the full and the reduced protocol during OGTT (*left panel*) and meal (*right panel*). Means ± SE, correlation plot, and Bland-Altman plot are shown. The line in the correlation plot represents the regression line, which is not statistically different from the identity line.**

both insulin secretion and action, thereby facilitating the conduct of large-scale epidemiologic studies and clinical trials. Whether a similar approach can be used in individuals with impaired insulin secretion (e.g., diabetes) awaits further study.

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REFERENCES

1. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667–E677, 1979
2. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C: Oral glucose tolerance test minimal model indexes of β-cell function and insulin sensitivity. *Diabetes* 50:150–158, 2001
3. Breda E, Toffolo G, Polonsky KS, Cobelli C: Insulin release in impaired glucose tolerance: oral minimal model predicts normal sensitivity to glucose but defective response times. *Diabetes* 51 (Suppl. 1):S227–S233, 2002
4. Dalla Man C, Caumo A, Cobelli C: The oral glucose minimal model: estimation of insulin sensitivity from a meal test. *IEEE Trans Biomed Eng* 49:419–429, 2002
5. Toffolo G, Breda E, Cavaghan MK, Ehrmann DA, Polonsky KS, Cobelli C: Quantitative indexes of beta cell function during graded up and down glucose infusion from C-peptide minimal models. *Am J Physiol* 280:E2–E10, 2001
6. Dalla Man C, Caumo A, Basu R, Rizza RA, Toffolo G, Cobelli C: Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method. *Am J Physiol* 287:E637–E643, 2004
7. Breda E, Robertson H, Caumo A, Yarasheski K, Chen X, Toffolo G,

Polonsky K, Cobelli C: Minimal model insulin sensitivity from oral glucose tolerance test: validation against hyperinsulinemic, euglycemic clamp (Abstract). *Diabetes* 51 (Suppl. 2):A350, 2002
8. Steil GM, Hwu CM, Janowski R, Hariri F, Jinagouda S, Darwin C, Tadros S, Rebrin K, Saad MF: Evaluation of insulin sensitivity and β-cell function indexes obtained from minimal model analysis of a meal tolerance test. *Diabetes* 53:1201–1207, 2004
9. Basu R, Breda E, Oberg A, Powell C, Dalla Man C, Arora P, Toffolo G, Cobelli C, Rizza R: Mechanisms of age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. *Diabetes* 52:1738–1748, 2003
10. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 68:1456–1467, 1981
11. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porter DJ: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
12. Basu A, Dalla Man C, Toffolo G, Basu R, Cobelli C, Rizza A: Effect of type 2 diabetes on meal glucose fluxes and insulin secretion (Abstract). *Diabetes* 53 (Suppl. 2):A579, 2004