Comparison of Estimates of Insulin Sensitivity From Minimal Model Analysis of the Insulin-Modified Frequently Sampled Intravenous Glucose Tolerance Test and the Isoglycemic Hyperinsulinemic Clamp in Subjects With NIDDM

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Minimal model (MINMOD) analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT) is dependent on an adequate insulin response to the glucose load. As this is characteristically deficient in subjects with non-insulin-dependent diabetes mellitus (NIDDM), the technique has been modified by the use of an intravenous bolus of insulin. Previous validation of this modification in humans has relied on agreement between insulin sensitivity indexes (S_I) estimated from tolbutamide- and insulin-modified tests and not on direct comparison with estimates derived from the isoglycemic glucose clamp. We have compared estimates of insulin sensitivity derived from minimal modeling of a 4-h insulin-modified FSIVGTT and the glucose clamp in subjects with NIDDM. Twelve subjects underwent an insulin-modified FSIVGTT and an isoglycemic hyperinsulinemic clamp in random order 2–4 weeks apart. Fasting plasma glucose (8.4 vs. 9.0 mmol/l) and immunoreactive insulin (IRI) concentrations (104.5 vs. 101.5 pmol/l) were not different between the 2 study days. $S_{I(clamp)}$ was derived from the steady-state glucose infusion rate during the 3rd h of the clamp, corrected for the ambient insulin and glucose concentrations. $S_{I(ivgtt)}$ was derived using MINMOD. $S_{I(ivgtt)}$ was 1.06 ± 0.18 $min^{-1} \cdot mU^{-1} \cdot ml \times 10^4$, and mean $S_{I(clamp)}$ was 4.97 ± 0.69 $l \cdot min^{-1}/pmol \cdot l^{-1} \times 10^4$ (mean ± SE). $S_{I(ivgtt)}$ was positively correlated with $S_{I(clamp)}$ ($r = 0.73$, $P = 0.004$) and negatively correlated with body mass index ($r = -0.7$, $P = 0.005$) and fasting $IRI_{(ivgtt)}$ ($r = -0.64$, $P = 0.008$). In summary, MINMOD analysis of the insulin-modified FSIVGTT provides a valid measure of insulin sensitivity in subjects with NIDDM.
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FSIVGTT, frequently sampled intravenous glucose tolerance test; IRAS, Insulin Resistance Atherosclerosis Study; IRI, immunoreactive insulin; MINMOD, minimal model; NIDDM, non-insulin-dependent diabetes mellitus; S_I, insulin sensitivity index.

Insulin resistance is increasingly being recognized as an important factor in the pathogenesis of a number of common diseases, including non-insulin-dependent diabetes mellitus (NIDDM) (1), ischemic heart disease (2), and hypertension (3). A wide range of techniques of varying degrees of complexity now exist for the estimation of insulin resistance, with the glucose clamp introduced by DeFronzo et al. (4) generally accepted as the standard against which others are compared. This technique uses the rate of glucose infused to maintain plasma glucose constant in the face of hyperinsulinemia as the basis of estimating insulin resistance. This procedure is labor-intensive and requires considerable expertise and equipment. The use of computer modeling of glucose and insulin dynamics during a frequently sampled intravenous glucose tolerance test (FSIVGTT)—the minimal model (MINMOD) technique—to derive an insulin sensitivity index (S_I) was introduced by Bergman et al. (5). This latter method offers advantages in terms of relative simplicity of the technique, with the only equipment requirements being a personal computer and the MINMOD program.

Early comparisons of the MINMOD technique with the glucose clamp in humans were disappointing, with only weak agreement between estimates from the two techniques (6,7). The difference was shown to be related to the magnitude of the endogenous insulin response to glucose (8). Subsequent modifications of the FSIVGTT with administration of tolbutamide to enhance endogenous insulin secretion to an intravenous glucose bolus in normal subjects (9,10) and the use of a higher dose of glucose (500 vs. 300 mg/kg) in both normal subjects and subjects with heart failure (11) have produced close correlations between clamp- and FSIVGTT-derived estimates of insulin resistance. Estimation of insulin resistance by the MINMOD technique has also been shown to be reproducible when repeated in the same individual (12–15).

The study of insulin resistance in subjects with NIDDM using MINMOD analysis of the FSIVGTT is limited by the characteristically poor early insulin responses of these subjects to intravenous glucose alone (16) and the variable response of the pancreatic β-cell response to sulfonylureas. These difficulties have, therefore, led many investigators to

use exogenous insulin following the glucose bolus to facilitate glucose disposal and aid modeling (17,18). Validation of this modification of the technique has been limited and largely dependent on comparisons with the tolbutamide-modified FSIVGTT or in subjects with insulin-dependent diabetes (17,19), although a previous study in NIDDM subjects showed a moderate correlation between the two techniques (20).

Therefore, we have examined the degree of correlation between estimates of insulin sensitivity from the insulin-modified FSIVGTT [$S_{I(ivgtt)}$] and the glucose clamp [$S_{I(clamp)}$] in subjects with established well-controlled NIDDM. We performed isoglycemic hyperinsulinemic clamps, with the subjects being clamped at their fasting glucose levels, to allow comparison with MINMOD estimates at comparable glycemia.

RESEARCH DESIGN AND METHODS

The study protocol was approved by the local ethics committee, and all participants gave written informed consent. Twelve men with established NIDDM agreed to take part. Their age was 59.6 ± 2.6 years; time since diagnosis, 6.3 ± 0.6 years; weight, 82 ± 41 kg; and body mass index, 28.1 ± 1.0 kg/m^2 (mean ± SE). No subject had any medical condition other than NIDDM or was receiving drugs other than sulfonylureas, and all were screened for fitness to participate by a full medical history and examination, routine biochemical and hematological screening, and electrocardiogram. Each subject underwent an insulin-modified FSIVGTT and an isoglycemic hyperinsulinemic clamp in random order with 2–4 weeks between tests, during which time study participants maintained their normal isocaloric diets. Sulfonylurea therapy was omitted on the study days.

Procedures

Isoglycemic hyperinsulinemic clamp. These studies took place after a 12-h overnight fast. An antecubital vein was cannulated and used for glucose and insulin infusions. Another cannula was inserted retrogradely into a contralateral hand vein, and the hand was warmed in a heated box to allow sampling of arterialized blood. After three basal samples for plasma glucose, an infusion of human Actrapid (Novo Nordisk, Bagsvaerd, Denmark) at a rate of 160 mU · min^{-1} · m^{-2} commenced for 4 min as a priming dose and then was reduced to 40 mU · min^{-1} · m^{-2}, which was maintained for the duration of the study. The plasma glucose concentration was clamped at basal (mean of the three basal plasma glucose values) by means of a variable infusion rate of 20% D-glucose, changed on the basis of plasma glucose concentrations obtained every 10 min, and analyzed on a YSI Y2300 glucose analyzer (Yellow Springs, OH). In addition to samples for plasma glucose, blood was drawn for the measurement of insulin in the basal period and at regular intervals during the procedure.

Various indexes of insulin sensitivity can be derived from clamp data. In the present study, without the use of radiolabeled glucose to assess hepatic glucose output, we derived $S_{I(clamp)}$, which reflects the glucose infusion rate to maintain euglycemia at steady state during the 3rd h of the clamp (M value), corrected for the change in insulin concentration from basal and the ambient glucose concentration ($M/\Delta I \times G$, where ΔI is the increment in insulin concentration from basal, and G is the clamped glucose concentration [21]). During this steady-state period, the mean ± SE plasma glucose concentration was 8.34 ± 0.67 mmol/l and the mean plasma insulin concentration was 575 ± 40 pmol/l. The mean coefficients of variation of steady-state plasma glucose and insulin concentrations were 3 ± 1 and 8 ± 3%, respectively.

Insulin-modified FSIVGTT. These studies were conducted after a 12-h overnight fast. Antecubital veins were cannulated in both arms, one for sampling and the other for administration of glucose and insulin. After basal sampling for glucose and insulin, glucose (300 mg/kg) was administered at a constant rate over 2 min from t = 0 min. At 20 min, 0.05 U/kg human Actrapid (Novo Nordisk) was given as a bolus injection. Blood samples for glucose and insulin were taken at t = 0, 2, 5, 8, 10, 12, 15, 20, 22, 24, 27, 30, 35, 45, 60, 90, 120, 150, 180, 210, and 240 min.

The insulin and glucose dynamics were modeled using the MINMOD (5) facilitated by the MINMOD computer program, which provides estimates of insulin sensitivity [$S_{I(ivgtt)}$] and glucose effectiveness, which reflects glucose disposal at basal insulin concentrations.

Analytical methods. Plasma glucose from the FSIVGTT was also assayed on the Y2300. Immunoreactive insulin (IRI) was measured by a modification of the technique of Heding (22) using a second antibody to separate free and antibody-bound ^{125}I-labeled insulin. The intra- and interassay coefficients of variation were 4.6 and 7.3%, respectively.

Statistical analysis. Analyses were conducted using SPSS/PC for Windows. Results are expressed as means ± SE unless stated otherwise. Linear regression analysis was used to derive the correlation coefficients; P values are one-sided.

TABLE 1
Insulin-modified FSIVGTT data

Subject	Basal insulin (pmol/l)	Basal glucose (mmol/l)	$SI_{(ivgtt)}$ (min^{-1} · mU^{-1} · ml × 10^4)
1	64	9.3	0.95
2	132	7.9	0.31
3	48	6.0	2.30
4	80	11.5	0.62
5	132	8.8	0.59
6	152	11.0	0.17
7	60	7.6	2.83
8	78	12.6	1.26
9	132	8.0	1.10
10	42	8.1	1.78
11	116	7.2	0.92
12	182	9.3	0.94
Means ± SE	101.5 ± 13.1	8.9 ± 0.6	1.06 ± 0.18

RESULTS

Table 1 includes data derived from the insulin-modified FSIVGTT, and Table 2 includes the data from the isoglycemic hyperinsulinemic clamp. Fasting plasma glucose and insulin concentrations were not different between the 2 study days (P = 0.12 and P = 0.64, respectively). Figure 1 shows the mean plasma glucose and plasma insulin concentrations during the FSIVGTT. $S_{I(ivgtt)}$ and $S_{I(clamp)}$ were highly correlated (r = 0.73, P = 0.004) (Fig. 2). $S_{I(ivgtt)}$ also correlated significantly with fasting insulin concentrations (r = −0.64, P = 0.008) and body mass index (r = −0.7, P = 0.005) (Fig. 3). Similarly, $S_{I(clamp)}$ was significantly correlated with both fasting insulin concentrations (r = −0.73, P = 0.005) and body mass index (r = −0.73, P = 0.004) (Fig. 4). $S_{I(ivgtt)}$ was also calculated using the more commonly used 180-min sampling time frame. Again, all plasma insulin and glucose profiles successfully modeled and derived a mean $S_{I(ivgtt\ 0-180)}$ of 1.03 ± 0.16 min^{-1} · mU^{-1} · ml × 10^4. This was not significantly different from $S_{I(ivgtt\ 0-240)}$ (P = 0.87) but correlated less well with $S_{I(clamp)}$ (r = 0.52, P = 0.04).

DISCUSSION

It is clear from earlier validation studies in normal subjects and subjects with various pathophysiological conditions that of the techniques available for the assessment of insulin action, i.e., the glucose clamp (4), continuous infusion of glucose with model assessment (23), the short insulin tolerance test (24), and MINMOD analysis of the FSIVGTT (5), all are intended to measure quantitatively the state of insulin sensitivity (25). Consequently, the choice of method depends on the aims and scope of the study and the investigators' preference. The glucose clamp has been widely exploited for the study of insulin resistance in subjects with NIDDM, but it is time-consuming and labor-intensive to conduct and there-

TABLE 2
Isoglycemic clamp data

Subject	Basal insulin (pmol/l)	Clamped insulin (pmol/l)	Basal glucose (mmol/l)	Clamped glucose (mmol/l)	M (mmol/min)	$SI_{(clamp)}$ ($l \cdot min^{-1}/pmol \cdot 1^{-1} \times 10^4$)
1	72	384	8.5	8.4	1.79	6.9
2	141	564	9.0	9.0	2.02	5.3
3	48	438	5.1	5.1	1.62	8.1
4	87	630	9.3	9.2	1.42	2.8
5	90	756	7.7	7.6	1.81	3.6
6	156	528	12.7	12.6	0.90	1.9
7	72	462	6.3	6.2	1.64	6.8
8	75	654	11.6	11.3	2.26	3.5
9	138	492	7.6	7.5	1.70	6.4
10	60	480	7.1	7.0	2.62	8.9
11	162	846	5.7	5.7	1.32	3.4
12	153	630	10.1	10.0	0.98	2.1
Means ± SE	104.5 ± 12.1	572 ± 39.4	8.4 ± 0.7	8.3 ± 0.7	1.67 ± 0.14	5.0 ± 0.7

fore suitable mainly when small numbers of subjects are involved. MINMOD analysis of glucose and insulin data from the FSIVGTT is also labor-intensive but is relatively simpler to conduct and provides estimates of both insulin sensitivity and glucose effectiveness, either or both of which may be pathophysiologically important in NIDDM (18). The insulin modification of the FSIVGTT also avoids the potential unpredictability of the quantitative and qualitative β-cell response to sulfonylureas in NIDDM subjects that is implicit in the tolbutamide-modified FSIVGTT. In this study, we have demonstrated that estimates of insulin sensitivity derived from the insulin-modified FSIVGTT correlate well with estimates of insulin sensitivity derived from the isoglycemic hyperinsulinemic clamp in the same individuals. It is also encouraging that both sets of estimates provide equally strong correlations with other factors known to be associated with insulin resistance, namely fasting plasma insulin concentration (1) and obesity (14,15,26).

Our findings merit comparison to those of the Insulin Resistance Atherosclerosis Study (IRAS) group (27). The IRAS group recently reported good agreement between clamp-derived and extended sampling protocol (n = 22)

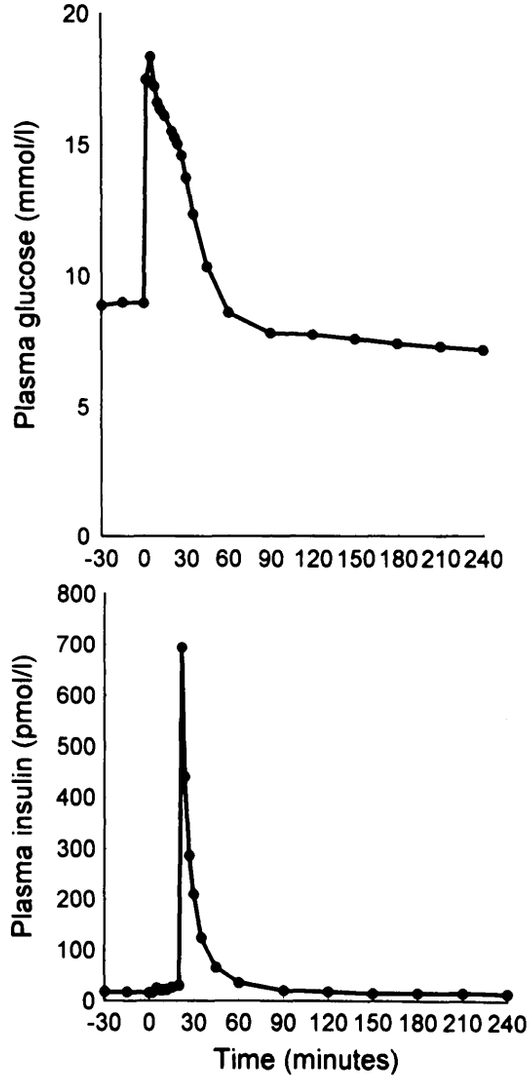

FIG. 1. Mean glucose and insulin concentration profiles during the FSIVGTT.

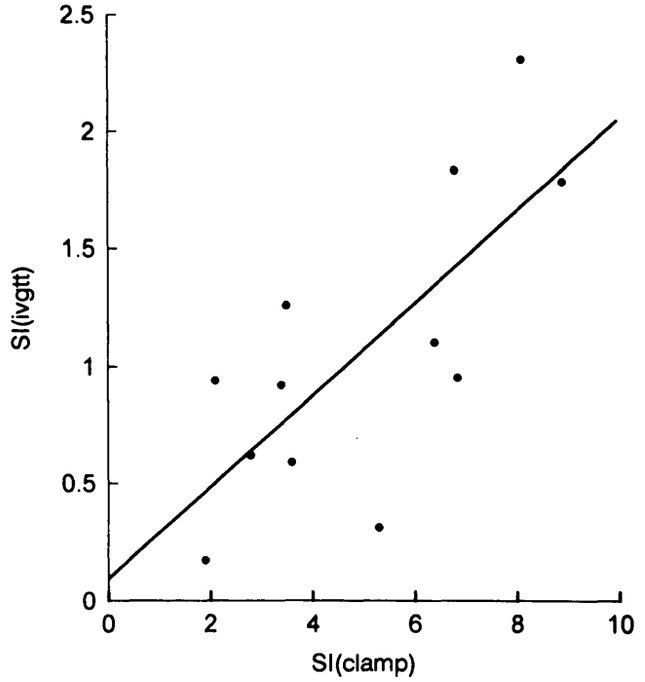

FIG. 2. Correlation between $S_{I(ivgtt)}$ and $S_{I(clamp)}$. r = 0.73; P = 0.004.

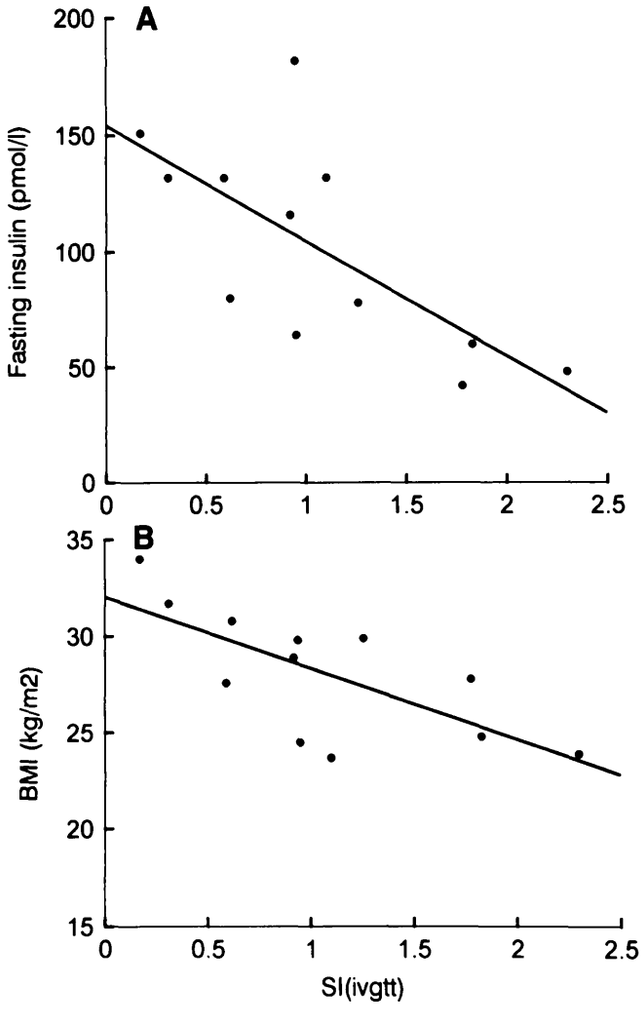

FIG. 3. Correlations between $S_{I(ivgtt)}$ and fasting insulin concentrations ($r = -0.64$; $P = 0.008$) (*A*) and body mass index ($r = -0.7$; $P = 0.005$) (*B*).

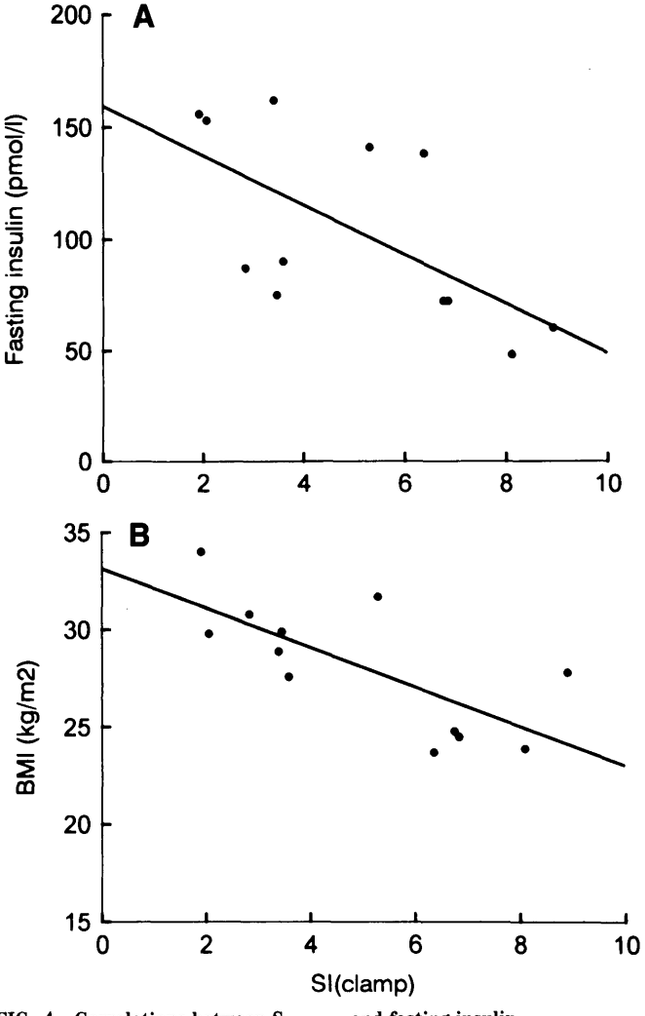

FIG. 4. Correlations between $S_{I(clamp)}$ and fasting insulin concentrations ($r = -0.73$; $P = 0.005$) (*A*) and body mass index ($r = -0.73$; $P = 0.004$) (*B*).

insulin-modified FSIVGTT-derived estimates of insulin sensitivity in normal healthy subjects ($r = 0.53$), although correlations were weaker in subjects with impaired glucose tolerance ($r = 0.48$) and NIDDM ($r = 0.41$). When the reduced sampling protocol ($n = 12$) was used in NIDDM subjects, no correlation with the clamp-derived estimates could be established ($r = 0.3$, $P = 0.085$). Importantly, in up to 50% of NIDDM subjects studied by the IRAS group, $S_{I(ivgtt)}$ could not be estimated with either the 12- or 22-sample procedures and was thus set to zero. Therefore, as a result of these findings, they recommended that the insulin-modified FSIVGTT be used in population studies involving nondiabetic populations only and that additional studies were needed before the routine use of this test in subjects with NIDDM.

In our study, we observed a greater correlation ($r = 0.73$, $P = 0.004$) than that observed by the IRAS group between estimates of insulin sensitivity from the insulin-modified FSIVGTT and the isoglycemic clamp in NIDDM subjects. The explanation for the discrepancy between these two study results despite the study of NIDDM subjects with similar characteristics (fasting plasma glucose, weight, and body mass index) must reside in the dose of insulin and the sampling schedule used in the insulin-modified FSIVGTT. We routinely use a higher dose of insulin than that used in the IRAS (0.05 vs. 0.03 U/kg), mainly because of concern over the marked insulin resistance of NIDDM subjects and in the absence of any published comparative data. Indeed, the insulin dose may be more important than the sampling schedule because when the FSIVGTT data were modeled using the more traditional 180-min sampling schedule, a slightly reduced, but still significant, agreement ($r = 0.52$, $P = 0.04$) for the estimates of insulin sensitivity between the two techniques was derived. This level of agreement was still greater, however, than that achieved in the IRAS, with all $S_{I(ivgtt\ 0-180)}$ values distinguishable from zero.

Our results demonstrate that the insulin-modified FSIVGTT with MINMOD analysis provides a valid measure of insulin sensitivity, justifying its continued use in the investigation of subjects with or at risk of developing NIDDM. For studies involving large numbers of NIDDM subjects or studies in which major changes in insulin sensitivity may be expected, the 180-min sampling schedule with the high-dose insulin bolus should suffice. However, for studies with small subject numbers or uncertainty about changes in insulin sensitivity, consideration should be given to the full 25-sample 240-min sampling schedule.

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