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Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity In Humans

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ABSTRACT

Insulin resistance plays an important role in the pathophysiology of diabetes and is associated with obesity and other cardiovascular risk factors. The "gold standard" glucose clamp and minimal model analysis are two established methods for determining insulin sensitivity *in vivo*, but neither is easily implemented in large studies. Thus, it is of interest to develop a simple, accurate method for assessing insulin sensitivity that is useful for clinical investigations. We performed both hyperinsulinemic isoglycemic glucose clamp and insulin-modified frequently sampled iv glucose tolerance tests on 28 nonobese, 13 obese, and 15 type 2 diabetic subjects. We obtained correlations between indexes of insulin sensitivity from glucose clamp studies (SI_{Clamp}) and minimal model analysis (SI_{MM}) that were comparable to previous reports ($r = 0.57$). We performed a sensitivity analysis on our data and discovered that physiological steady state values [*i.e.* fasting insulin (I_0) and glucose (G_0)] contain critical information about insulin sensitivity. We defined a quantitative insulin sensitivity check index ($QUICKI = 1/[\log(I_0) + \log(G_0)]$) that has substantially better correlation with SI_{Clamp} ($r = 0.78$) than the correlation we observed between SI_{MM} and SI_{Clamp}. Moreover, we observed a comparable overall correlation between QUICKI and SI_{Clamp} in a totally independent group of 21 obese and 14 nonobese subjects from another institution. We conclude that QUICKI is an index of insulin sensitivity obtained from a fasting blood sample that may be useful for clinical research. (*J Clin Endocrinol Metab* **85:** 2402–2410, 2000)

INSULIN IS A key regulator of glucose homeostasis. Insulin resistance (decreased sensitivity or responsiveness to the metabolic actions of insulin) is determined by both genetic and environmental factors and plays an important pathophysiological role in diabetes (1, 2). In addition, insulin resistance is associated with a number of other diseases, including obesity, hypertension, dyslipidemias, and coronary artery disease (3–6). Therefore, the ability to easily quantify insulin sensitivity in large numbers of subjects may be useful for investigating the role of insulin resistance in the pathophysiology of these major public health problems.

The hyperinsulinemic euglycemic glucose clamp technique is the "gold standard" for quantifying insulin sensitivity *in vivo* because it directly measures the effects of insulin to promote glucose utilization under steady state conditions (7, 8). However, the glucose clamp is not easily applied in large scale investigations because iv infusion of insulin, frequent blood samples over a 3-h period, and continuous adjustment of a glucose infusion are required for each subject studied. A well accepted alternative for estimating insulin sensitivity involves minimal model analysis of a frequently sampled iv glucose tolerance test (FSIVGTT) (9–11). Although this approach is less labor intensive than the glucose clamp, the FSIVGTT is still not ideal for large studies because it requires obtaining approximately 30 blood samples over 3 h. Furthermore, although the minimal model index of insulin sensitivity (SI_{MM}) generally correlates with glucose clamp measurements (Table 1), identification of SI_{MM} in subjects with impaired insulin secretion (*e.g.* patients with diabetes) is often problematic (12). Moreover, recent studies have demonstrated systematic errors in minimal model estimates of glucose effectiveness and insulin sensitivity that may be due to oversimplified model representations of physiology (13–15).

In the present study we performed both glucose clamp and FSIVGTT studies in 28 nonobese, 13 obese, and 15 diabetic subjects. After performing a sensitivity analysis on data from an initial subset of subjects, we derived a novel quantitative insulin sensitivity check index (QUICKI) that can be determined from a fasting blood sample. Importantly, QUICKI could be identified for all study subjects, and the correlation of QUICKI with glucose clamp measures of insulin sensitivity was significantly better than the correlation between SI_{MM} and the glucose clamp.

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Subjects and Methods

This study was approved by the institutional review board of the National Heart, Lung, and Blood Institute. Informed consent was obtained from each subject. Each subject underwent a glucose clamp study and an insulin-modified FSIVGTT. Studies in the same subject were performed at least 1 week apart, and the order of the studies was

TABLE 1. Summary of previously published studies comparing estimates of insulin sensitivity derived from the glucose clamp technique with minimal model analysis

Reference no.	Subjects	Insulin dose ($mU/m^2 \cdot min$)	Clamp period (min)	Clamp sensitivity	FSIVGTT method	r
32	12 N	2, 25	30	$\Delta R_d/(\Delta I \times G)$	Standard	0.44
33	9 N, 3 IGT, 8 DM; 11 ♂, 9♀	40	120	MCR	Standard	0.53
34	10 N ♂	8, 16	40	$\Delta R_d/(\Delta I \times G)$	Standard	0.54
34	10 N ♂	8, 16	40	$\Delta R_d/(\Delta I \times G)$	Tolbutamide-modified	0.84
9	5 N, 5 Ob, 9 ♂, 1♀	0, 15, 40	40	$\Delta R_d/(\Delta I \times G)$	Tolbutamide-modified	0.89
35	6 N, 6 Ob, 8 ♂, 4♀	~60	30	M/I	Standard, Abbreviated	0.85
12	11 N, 20 IGT, 24 DM 40♂, 15♀	0, 40	40	R_d/G	Insulin-modified (bolus)	0.62
12	11 N, 8 ♂, 3♀	0, 40	40	R_d/G	Insulin-modified (bolus)	0.53
12	20 IGT, 14 ♂, 6♀	0, 40	40	R_d/G	Insulin-modified (bolus)	0.48
12	12 DM (24 attempted)	0, 40	40	R_d/G	Insulin-modified (bolus)	0.41
36	10 N, 5 heart failure 14 ♂, 1♀	40	20	$\Delta R_d/(\Delta I \times G)$	Standard (500 mg/kg glucose)	0.92
37	12 DM ♂	40	60	$M/(\Delta I \times G)$	Insulin-modified (bolus)	0.73
38	14 N ♀	0	60, hyperglycemic	M/I	Tolbutamide-modified	0.88
39	11 N, 20 IGT, 24 DM 40 ♂, 15♀	40	60	$M/(\Delta I \times G)$	Insulin-modified (bolus)	?
11	35 N ♂	40	40	$M/(\Delta I \times G)$	Insulin-modified (bolus)	0.70
11	35 N ♂	40	40	$M/(\Delta I \times G)$	Tolbutamide-modified	0.71

N, Normal; Ob, obese; IGT, impaired glucose tolerance; DM, type 2 diabetes ♂, male; ♀ female; R_d, glucose disposal rate during clamp; I, insulin; G, glucose; Δ, difference between baseline and steady state; M, glucose infusion rate during steady state; MCR of glucose (R_d − urinary glucose/G); r, correlation coefficient between glucose clamp and minimal model studies.

TABLE 2. Clinical characteristics of study subjects

Group	Gender	Age (yr)	BMI (kg/m^2)	Fasting glucose (mg/dL)	Fasting insulin ($\mu U/mL$)
Nonobese	15♂,13♀	31 ± 2	24.2 ± 0.5	83 ± 2	6 ± 1
Obese	5♂, 8♀	41 ± 3	38.6 ± 1.7	88 ± 2	16 ± 3
DM	7♂, 8♀	46 ± 2	35.1 ± 2.9	161 ± 15	15 ± 2

Data shown are the mean ± SEM from the glucose clamp studies

randomized. All diabetic subjects were taken off of their antidiabetic medications for 1 week before each test.

Subjects

Our study included 28 nonobese, 13 obese, and 15 diabetic subjects whose clinical characteristics are listed in Table 2. Among these subjects were 38 Caucasians, 11 African-Americans, 5 Asians, and 2 Hispanics. Nonobese subjects were defined as having a body mass index (BMI) less than 30 kg/m^2, whereas subjects with a BMI of 30 or more were considered obese. Diabetic subjects met the American Diabetes Association criteria for type 2 diabetes (16). Subjects with liver or pulmonary disease as well as end-organ damage, such as renal insufficiency, coronary artery disease, heart failure, peripheral vascular disease, proliferative retinopathy, or diabetic neuropathy, were excluded from our study. In addition, diabetic patients whose fasting blood glucose exceeded 300 mg/dL while not taking medication were excluded from our study. We also obtained an independent dataset from the Division of Endocrinology and Metabolism at Indiana University School of Medicine. This comprised glucose clamp data obtained from 21 obese subjects (BMI, 37.3 ± 1.1; age, 35 ± 2 yr) and 14 nonobese subjects (BMI, 24.6 ± 0.9; age, 36 ± 2 yr) using an insulin infusion rate of 120 $mU/m^2 \cdot min$.

Hyperinsulinemic isoglycemic glucose clamp

At approximately 0800 h, after an overnight fast of at least 10 h, subjects were admitted as out-patients to the Clinical Center at NIH and placed in a recumbent position in an adjustable bed. An iv catheter was placed in an antecubital vein for infusion of insulin, glucose, and potassium phosphate. Another catheter was placed in the contralateral hand for blood sampling. The hand used for sampling was warmed with a heating pad to arterialize the blood. An insulin solution (regular Humulin, Eli Lilly & Co., Indianapolis, IN) was prepared with normal saline at a concentration ranging from 0.8–1.2 U/mL. The insulin solution was allowed to dwell in the iv lines for at least 15 min, and the lines were then flushed before the beginning of the insulin infusion. Insulin was infused at 120 $mU/m^2 \cdot min$ for 4 h using a calibrated syringe pump (model A-99, Razel Industries, Stamford, CT). A solution of potassium phosphate was infused at the same time (0.23 $mEq/kg \cdot h$) to prevent hypokalemia. Blood glucose concentrations were measured at the bedside every 5–10 min using a glucose analyzer (YSI 2700 Select, YSI, Inc., Yellow Springs, OH), and an infusion of 20% dextrose was adjusted to maintain the blood glucose concentration at the fasting level. Blood samples were also collected every 20–30 min for determination of plasma insulin concentrations (IMX assay, Abbott Laboratories, North Chicago, IL). The steady state period of the clamp was defined as a 60-min or longer period (at least 1 h after the beginning of the insulin infusion) during which the coefficient of variations for blood glucose, plasma insulin, and glucose infusion rate were less than 5%. The glucose clamp-derived index of insulin sensitivity (SI_{Clamp}) was defined as $M/(G \times \Delta I)$ corrected for body weight (where M is the steady state glucose infusion rate (milligrams per min), G is the steady state blood glucose concentrations (milligrams per dL), and ΔI is the difference between basal and steady state plasma insulin concentrations (microunits per mL)).

FSIVGTT and minimal model analysis

At approximately 0800 h, after an overnight fast of at least 10 h, subjects were admitted as out-patients to the Clinical Center at NIH and placed in a recumbent position in an adjustable bed. Intravenous catheters were placed in the antecubital vein of each arm. An insulin-modified FSIVGTT was performed as described previously (17). Briefly, a bolus of glucose (0.3 g/kg) was infused iv over 2 min. Twenty minutes after initiation of the glucose bolus, an iv infusion of insulin (4 $mU/kg \cdot min$ regular Humulin) was given for 5 min. Blood samples were collected for blood glucose and plasma insulin determinations as previously described (17). Data were subjected to minimal model analysis using the computer program MINMOD (gift from R. N. Bergman) to generate predictions of glucose disappearance and insulin sensitivity (SI_{MM}) (10).

QUICKI

We performed a sensitivity analysis of glucose and insulin data from the glucose clamp and the first 20 min of the FSIVGTT of an initial subset of 14 normal, 5 obese, and 3 diabetic subjects to determine the time points that contained the most critical information related to insulin sensitivity as defined by SI_{Clamp}. We found that changes in fasting insulin and glucose levels were the most related to changes in SI_{Clamp}. We subjected the fasting data to various transformations and ultimately defined $QUICKI = 1/[\log(I_0) + \log(G_0)]$, where I_0 is the fasting insulin, and G_0 is the fasting glucose. After QUICKI was derived from the initial subset

of data, comparisons between QUICKI and the other indexes of insulin sensitivity were performed on the entire set of 28 nonobese, 13 obese, and 15 diabetic subjects. We also calculated QUICKI for the 21 obese and 14 nonobese subjects from Indiana University School of Medicine.

Statistical analysis

Student's *t* tests were used to compare differences between various parameters when appropriate. Correlations (r) between pairs of indexes of insulin sensitivity were calculated. To evaluate the significance of differences in r values for various pairs of indexes, a percentile method bootstrap technique was used to calculate *P* values (18). The bootstrap was necessary because the r values were based on the same subjects, and thus, pairs of r values are not statistically independent. $P < 0.05$ was considered to indicate statistical significance.

Results

Study subjects

Mean BMI, fasting glucose, and fasting insulin values were calculated for each group of subjects (Table 2). Both obese and diabetic subjects had significantly greater BMIs and fasting insulin levels than the nonobese subjects ($P < 6 \times 10^{-6}$), consistent with the presence of obesity and insulin resistance. As expected, the fasting glucose levels for both nonobese and obese groups were normal, whereas the diabetic group had elevated levels.

Glucose clamp studies

To determine the insulin sensitivity of each subject using the gold standard method, hyperinsulinemic isoglycemic glucose clamps were performed using an insulin infusion rate of 120 mU/m^2·min (Fig. 1). Steady state conditions were generally achieved about 2 h after the initiation of each study and were maintained for at least 60 min. During the steady state period, the mean blood glucose levels were 85 ± 2 mg/dL for nonobese subjects, 86 ± 3 for obese subjects, and 158 ± 15 for diabetic subjects. The steady state plasma insulin levels were 272 ± 24, 334 ± 22, and 286 ± 19 μU/mL for nonobese, obese, and diabetic subjects, respectively, while the glucose infusion rates were 870 ± 50 (nonobese subjects), 802 ± 64 (obese subjects), and 900 ± 94 mg/min (diabetic subjects). The mean values for SI_{Clamp} calculated from these data were 6.19 ± 0.43 (nonobese subjects), 2.94 ± 0.42 (obese subjects), and 2.39 ± 0.26 (diabetic subjects). Thus, as expected, the obese and diabetic subjects were significantly more insulin resistant than the nonobese subjects ($P < 2 \times 10^{-5}$). For nine nonobese subjects, the glucose clamp studies were repeated using a lower insulin infusion rate (40 mU/m^2·min) that gave a mean steady state blood glucose level of 82 ± 2 mg/dL, a mean plasma insulin level of 72 ± 3 μU/mL, and a mean glucose infusion rate of 621 ± 81 mg/min. The correlation between glucose clamps with high and low insulin infusion rates for these nine subjects was very good (r = 0.69; $P < 0.04$).

Insulin-modified FSIVGTT studies

To calculate an alternative insulin sensitivity index for each subject based on minimal model analysis, insulin-modified FSIVGTTs were performed (Fig. 2). Both nonobese and obese subjects had normal basal glucose levels (83 ± 2 and 88 ± 2 mg/dL, respectively). The basal glucose levels in the diabetic group were significantly elevated compared with those in the other groups (166 ± 15 mg/dL; $P < 4 \times 10^{-5}$). The basal insulin levels were 7 ± 1, 17 ± 3, and 15 ± 2 μU/mL for the nonobese, obese, and diabetic groups, respectively. The basal insulin levels in both the obese and diabetic groups were significantly higher than those in the normal group ($P < 0.02$). In addition, endogenous insulin secretion (0–20 min) in response to the iv glucose bolus in obese subjects was greater than that in nonobese subjects (mean insulin peak, 157 ± 34 *vs.* 100 ± 14 μU/mL; $P < 0.04$), whereas the insulin response was markedly diminished in the diabetic subjects. When glucose and insulin data from the FSIVGTT were analyzed using the MINMOD program, minimal model predictions of glucose disappearance fit well with the actual glucose disappearance data (Fig. 2). The minimal model index of insulin sensitivity (SI_{MM}) was 5.3 ± 0.6 for nonobese subjects, 3.5 ± 1.2 for obese subjects, and 4.8 ± 1.0 for diabetic subjects. Note that for 7 of the 15 diabetic subjects, minimal model analysis generated large negative values for SI_{MM} (implying that rises in insulin somehow cause glucose levels to increase in these subjects). This is a well documented artifact of the minimal model that occurs when data from subjects with poor insulin secretion are

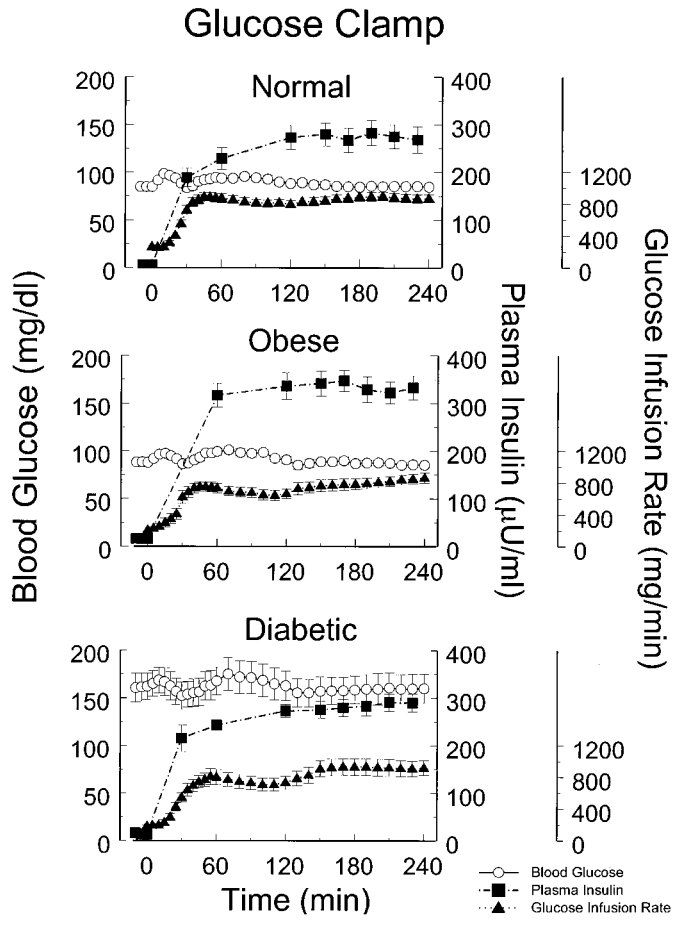

FIG. 1. Hyperinsulinemic isoglycemic glucose clamp studies in 28 nonobese (*top*), 13 obese (*middle*), and 15 diabetic (*bottom*) subjects. Data shown are the mean ± SEM for blood glucose concentration (○), plasma insulin concentration (■), and glucose infusion rate (▲) plotted as a function of time.

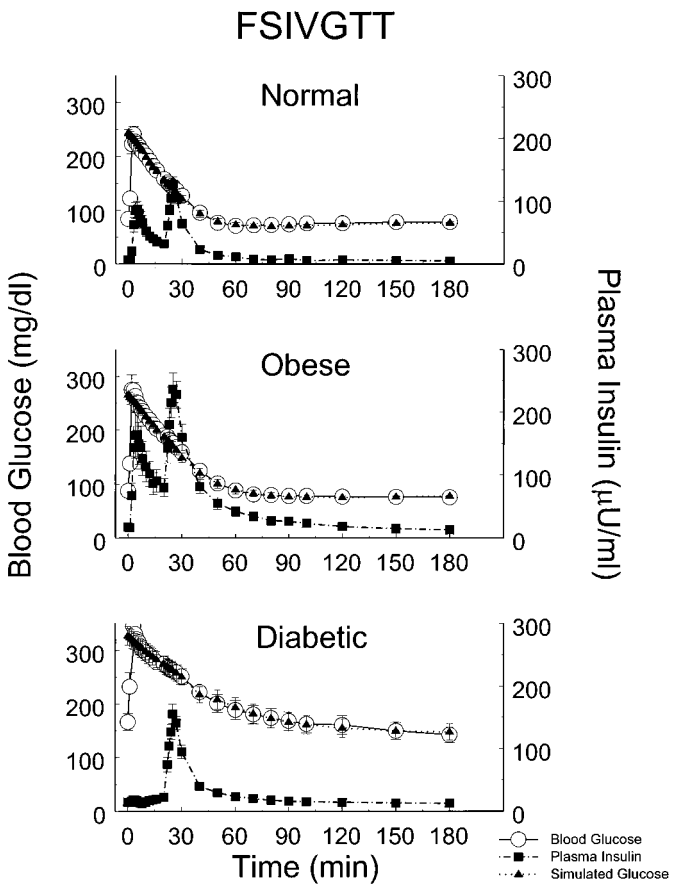

FIG. 2. Insulin-modified FSIVGTTs in 28 nonobese (*top*), 13 obese (*middle*), and 15 diabetic (*bottom*) subjects. Data shown are the mean ± SEM for blood glucose concentration (○), plasma insulin concentration (■), and minimal model simulation of glucose concentration (▲) plotted as a function of time.

analyzed (12). Therefore, the minimal model results for these 7 diabetic subjects were excluded from our analyses.

QUICKI

To derive a novel index of insulin sensitivity, we analyzed data obtained from an initial subset of studies in 14 nonobese, 5 obese, and 3 diabetic subjects. We used a sensitivity analysis to determine which data points from the first 20 min of the FSIVGTT contained the most information about insulin sensitivity as determined by SI_{Clamp}. For nonobese and obese subjects, we discovered that fasting insulin levels correlated well with SI_{Clamp}. Moreover, because fasting insulin levels had a skewed distribution, log transformation of these data was even more highly correlated with SI_{Clamp}. This result is consistent with the reasoning that fasted nondiabetic subjects are in a steady state in which normal glucose levels are maintained by appropriately adjusting insulin levels to match the degree of insulin sensitivity. However, this relationship between fasting insulin and SI_{Clamp} is not maintained for diabetic subjects who have fasting hyperglycemia and are unable to appropriately secrete insulin to fully compensate for their insulin resistance. Interestingly, we found that the product of fasting insulin and glucose yielded an index of insulin sensitivity that was applicable to both diabetic and nondiabetic subjects. To obtain a positive correlation with SI_{Clamp} and transform the data further, we took the reciprocal of this product. Thus, we defined the QUICKI as: $QUICKI = 1/[(\log(I_0) + \log(G_0)]$, where I_0 is the fasting plasma insulin level (microunits per mL), and G_0 is the fasting blood glucose level (milligrams per dL). Subsequent to our initial sensitivity analysis of the first subset of subjects, as described above, QUICKI was calculated for all study subjects (mean, 0.382 ± 0.007, 0.331 ± 0.010, and 0.304 ± 0.007 for nonobese, obese, and diabetic subjects, respectively).

Correlations between indexes of insulin sensitivity

We first compared our glucose clamp-derived estimates of insulin sensitivity with those obtained from minimal model analysis (Fig. 3). The overall correlation coefficient (r) calculated from a linear least squares regression was 0.57 ($P < 2 \times 10^{-5}$). When each group was analyzed separately, we found that r = 0.48 for nonobese subjects ($P < 0.01$), r = 0.82 for obese subjects ($P < 6 \times 10^{-4}$), and r = 0.51 for diabetic subjects ($P < 0.2$). In addition, linear regression analysis for the subgroups showed regression lines that were parallel to the overall regression line but shifted up for the nonobese subgroup and shifted down for the obese and diabetic subgroups. However, the parallel relationship between regression lines may not be significant because of the large variability observed in the nonobese group. As expected, correlations between our glucose clamp and FSIVGTT studies gave results comparable to those of previously published studies (*c.f.* Table 1).

We next compared our novel index, QUICKI, with SI_{Clamp} (Fig. 4). When QUICKI was calculated using the average data from two fasting blood samples obtained at −10 and 0 min of the glucose clamp study (*i.e.* before the administration of insulin) we found that QUICKI and SI_{Clamp} were highly correlated for all subjects (r = 0.78; $P < 2 \times 10^{-12}$). Similar results were obtained when QUICKI was derived from a single blood sample (r = 0.71; $P < 6 \times 10^{-10}$). Note that in contrast to the minimal model-derived SI_{MM}, we were able to calculate meaningful values of QUICKI for all diabetic subjects studied. More importantly, the overall correlation between QUICKI and SI_{Clamp} was significantly better than that between SI_{MM} and SI_{Clamp} ($P < 0.028$). However, we could only calculate the P value for the differences between these two correlations for the 49 subjects for whom we had complete information on all three methods. In this case, r = 0.74 for the comparison between QUICKI and SI_{Clamp}. As r = 0.78 when all 56 subjects are included for this comparison, the significance of the difference between correlations of QUICKI with SI_{Clamp} and of SI_{MM} with SI_{Clamp} is even greater than the value we calculated. We also assessed the interassay reproducibility of QUICKI by comparing SI_{Clamp} to QUICKI derived from baseline blood samples obtained during the FSIVGTT (performed at least 1 week apart from the glucose clamp). Reassuringly, in these independent studies, we found that the overall correlation between QUICKI and SI_{Clamp} was similar to that in our original analysis (r = 0.77; $P < 2 \times 10^{-11}$). When correlations between QUICKI and SI_{Clamp} were calculated for each group separately, we found

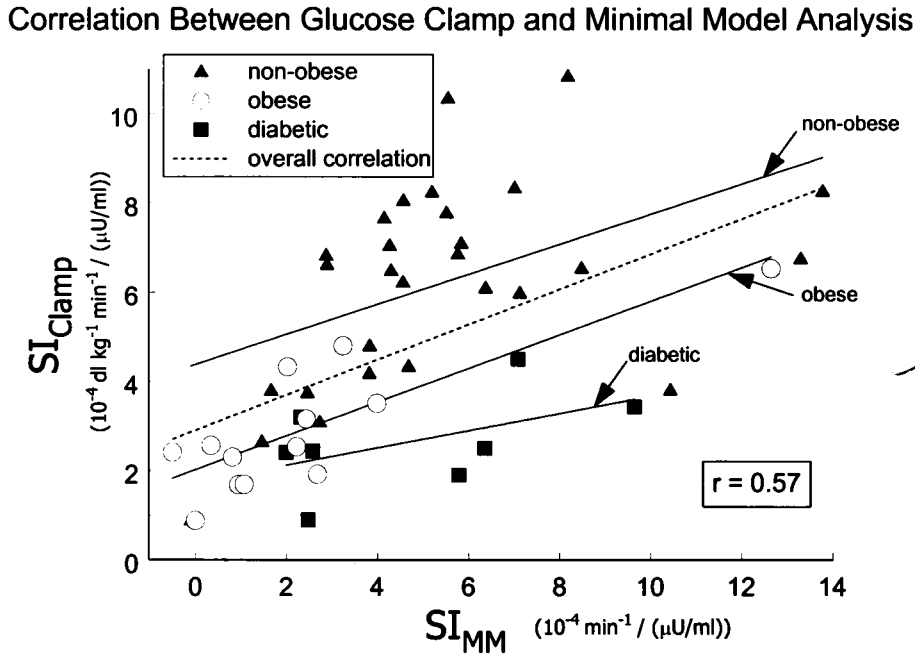

FIG. 3. Correlation between glucose clamp and minimal model indexes of insulin sensitivity. SI_{Clamp} and SI_{MM} were determined as described in *Subjects and Methods*. Indexes are plotted for 28 nonobese subjects (△), 13 obese subjects (○), and 8 diabetic subjects (■). Note that nonsensical values for SI_{MM} were obtained in 7 of 15 diabetic subjects; thus, their results were excluded from this analysis. The *dashed line* represents the linear regression between SI_{Clamp} and SI_{MM} for all subjects (r = 0.57; $P < 2 \times 10^{-5}$). When each group was analyzed separately, r = 0.48 (P = 0.01) for nonobese subjects, 0.82 ($P < 6 \times 10^{-4}$) for obese subjects, and 0.51 (P = 0.03) for diabetic subjects. Linear regression lines are also shown for the subgroup analysis.

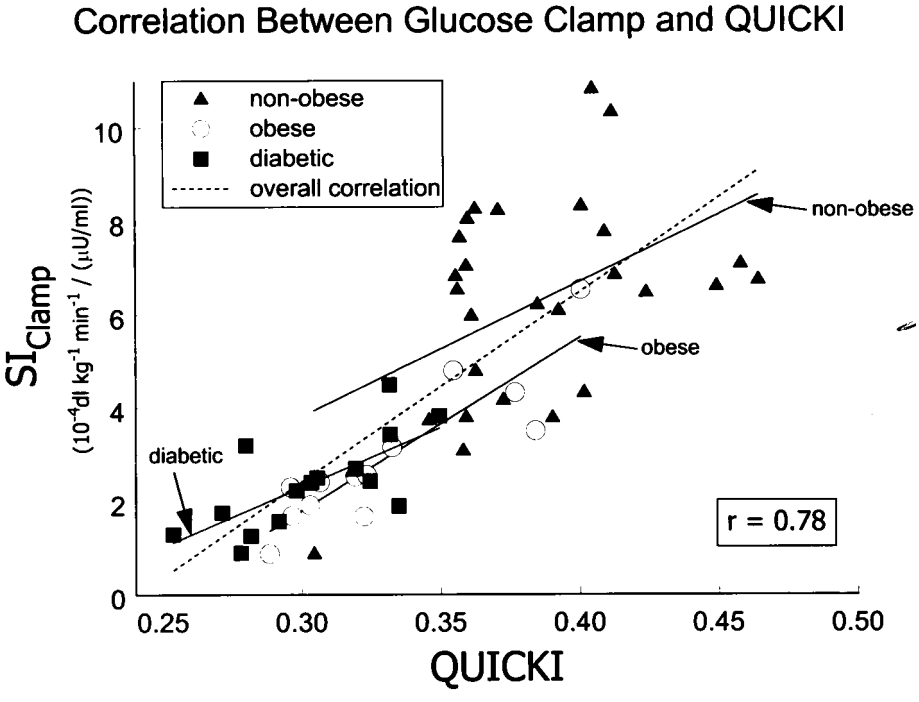

FIG. 4. Correlation between SI_{Clamp} and QUICKI. Indexes are plotted for 28 nonobese subjects (△), 13 obese subjects (○), and 15 diabetic subjects (■). QUICKI was calculated from fasting glucose and insulin values obtained from glucose clamp studies. The *dashed line* represents the linear regression between SI_{Clamp} and QUICKI for all subjects (r = 0.78; $P < 2 \times 10^{-12}$). When each group was analyzed separately, r = 0.49 ($P < 0.01$) for nonobese subjects, 0.89 ($P < 2 \times 10^{-5}$) for obese subjects, and 0.7 ($P < 4 \times 10^{-3}$) for diabetic subjects. Linear regression lines are also shown for the subgroup analysis. Comparable results were obtained when QUICKI was calculated from data obtained during the FSIVGTT (overall r = 0.77; $P < 2 \times 10^{-11}$).

that r = 0.49 for nonobese subjects ($P < 0.01$), r = 0.89 for obese subjects ($P < 2 \times 10^{-5}$), and r = 0.7 for diabetic subjects ($P < 4 \times 10^{-3}$). The linear regression lines for the subgroup analysis followed the overall regression more closely than when SI_{Clamp} was compared with SI_{MM}. When QUICKI and SI_{Clamp} were compared for the nine nonobese subjects who were studied at the lower insulin infusion rate, r = 0.30. To validate QUICKI with a completely independent dataset, we also correlated QUICKI with SI_{Clamp} using data from Indiana University School of Medicine. This analysis yielded r = 0.74 for obese subjects (n = 21) and r = 0.91 for nonobese subjects (n = 14), with an overall correlation coefficient of r = 0.90 (n = 35). Interestingly, among these nonobese subjects, one individual had an extremely low BMI of 19.3 kg/m^2 with a fasting insulin level of 1.05 μU/mL. If the data from this individual were excluded from the analysis, the overall correlation between QUICKI and SI_{Clamp} would be r = 0.77 (n = 34).

When QUICKI was compared with SI_{MM}, we found that the overall correlation between these two indexes (r = 0.52; $P < 2 \times 10^{-5}$) was comparable to the correlation obtained between SI_{Clamp} and SI_{MM} (Fig. 5). When correlations between QUICKI and SI_{MM} were calculated for each group separately, we found that r = 0.36 for nonobese subjects ($P <$

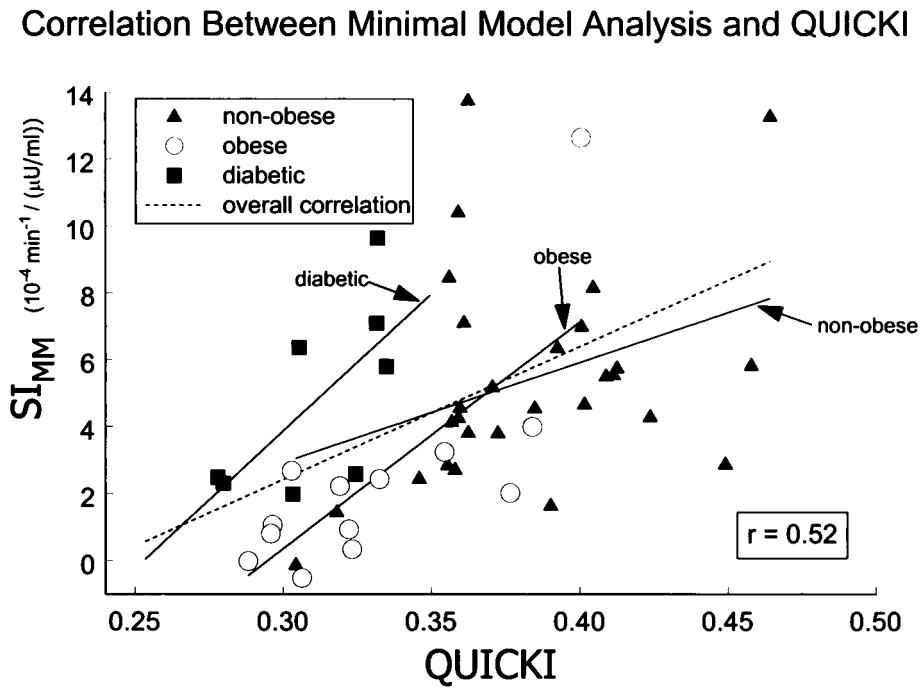

FIG. 5. Correlation between SI_{MM} and QUICKI. Indexes are plotted for 28 nonobese subjects (△), 13 obese subjects (○), and 8 diabetic subjects (■). Note that nonsensical values for SI_{MM} were obtained in 7 of 15 diabetic subjects; thus, their results were excluded from this analysis. QUICKI was calculated from fasting glucose and insulin values obtained from glucose clamp studies. The *dashed line* represents the linear regression between SI_{MM} and QUICKI for all subjects ($r = 0.52$; $P < 2 \times 10^{-4}$). Linear regression lines are also shown for the subgroup analysis. Comparable results were obtained when QUICKI was calculated from data obtained during the FSIVGTT (overall $r = 0.59$; $P < 2 \times 10^{-5}$).

TABLE 3. Overall correlation coefficients (r) between various indexes of insulin sensitivity derived from our data obtained during glucose clamp and FSIVGTT studies

	SI_{clamp}	SI_{MM}	QUICKI	HOMA
SI_{Clamp}	1			
SI_{MM}	0.57	1		
QUICKI	0.78	0.52	1	
HOMA	0.6	0.5	0.77	1

SI_{Clamp}, SI_{MM}, and QUICKI were calculated as described in *Materials and Methods.* HOMA is defined as (fasting insulin × fasting glucose)/22.5. Because HOMA is negatively correlated with insulin sensitivity, the sign of HOMA was reversed when calculating correlation coefficients between HOMA and SI_{Clamp} or QUICKI.

0.07), $r = 0.75$ for obese subjects ($P < 4 \times 10^{-3}$), and $r = 0.67$ for diabetic subjects ($P < 0.07$). However, linear regression analysis for the subgroups revealed that the regression line for the diabetic and obese subgroups had a very different slope than that for the nonobese group. Because QUICKI bears some similarities to a previously reported insulin sensitivity index derived from the so-called homeostasis model assessment (HOMA) (19, 20) we also compared SI_{Clamp}, SI_{MM}, and QUICKI with HOMA (calculated as (fasting insulin × fasting glucose)/22.5) (Table 3). Interestingly, although HOMA was highly correlated with QUICKI, the overall correlation between the gold standard SI_{Clamp} and QUICKI was still significantly better than the overall correlation between SI_{Clamp} and HOMA ($P < 0.004$). As HOMA becomes larger with decreased insulin sensitivity, we compared SI_{Clamp} with HOMA to obtain a positive correlation (Fig. 6). Strikingly, linear regression analysis of the subgroups showed that the nonobese group had a regression line with a very steep slope, whereas the obese group had a more moderate slope, and the diabetic group had a very shallow slope. These results suggest that HOMA does not vary linearly across wide ranges of insulin sensitivity and patient groups. Indeed, the correlation between log [HOMA] and QUICKI was very high ($r = 0.98$).

Discussion

Glucose clamp and minimal model estimates of insulin sensitivity

We performed both hyperinsulinemic isoglycemic glucose clamps and insulin-modified FSIVGTTs in nonobese, obese, and diabetic subjects with a wide range of insulin sensitivities. As expected, when subjects were evaluated with the gold standard glucose clamp method, obese subjects were more insulin resistant, on the average, than nonobese subjects, and diabetics were the most insulin-resistant group. In contrast, when the same subjects underwent FSIVGTT and minimal model analysis, the obese group seemed to have the greatest level of insulin resistance. This is most likely due to the fact that 7 of 15 diabetic subjects had to be excluded from analysis because the minimal model was unable to identify meaningful estimates of insulin sensitivity in these cases. Indeed, these 7 excluded subjects had higher levels of insulin resistance than the other diabetic subjects (as assessed by glucose clamp). The inability of the minimal model to identify meaningful values for SI_{MM} in a large fraction of our diabetic subjects is consistent with the experience of others and is most likely related to well described difficulties in estimating SI_{MM} under conditions of inadequate insulin secretion (12). The overall correlation we obtained between SI_{Clamp} and SI_{MM} was comparable to previous reports whose study subjects included diabetics, suggesting that our studies were technically adequate. Nevertheless, the level of correlation obtained between direct measures of insulin sensitivity (*i.e.* glucose clamp) and indirect measures, such as minimal model analysis, in both the present study and previous studies suggests that investigators should be cautious in

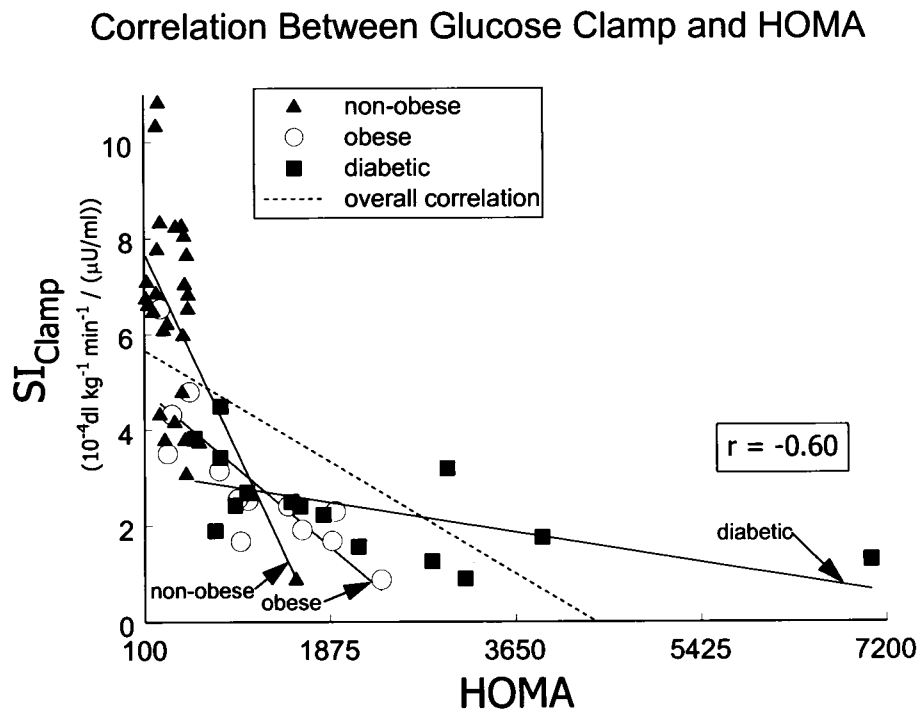

FIG. 6. Correlation between SI_{Clamp} and HOMA. Indexes are plotted for 28 nonobese subjects (△), 13 obese subjects (○), and 15 diabetic subjects (■). HOMA was calculated from fasting glucose and insulin values obtained from glucose clamp studies. The *dashed line* represents the linear regression between SI_{Clamp} and HOMA for all subjects ($r = 0.60$; $P < 2 \times 10^{-4}$). Linear regression lines are also shown for the subgroup analysis.

applying minimal model analysis of insulin sensitivity to population studies. This is further highlighted by recent studies demonstrating particular inadequacies of the minimal model approach that result in overestimation of glucose effectiveness and underestimation of insulin sensitivity (14, 17).

Although the glucose clamp is considered to be the gold standard method for directly measuring insulin sensitivity *in vivo,* it can be implemented in a number of different ways. We chose to use a single, relatively high, insulin infusion rate (120 mU/m^2·min) because we anticipated that our diabetic and obese subjects would have significant insulin resistance. That is, achieving a high steady state insulin level in these subjects may be required to measure a significant effect of insulin on net glucose disposal. To help ensure that these conditions were also appropriate for nonobese subjects, we repeated studies in nine nonobese subjects using a lower insulin infusion rate (40 mU/m^2·min). The good correlation we obtained between studies performed at low and high insulin infusion rates suggests that the higher insulin infusion rate was also appropriate for the nonobese subjects. We decided to clamp glucose levels at the fasting value (isoglycemic clamp) rather than at normal levels (euglycemic clamp) because acute changes in insulin sensitivity related to large changes in glycemia may complicate the interpretation of glucose clamp results. In the case of nonobese and obese subjects who had normal fasting glucose levels, the isoglycemic clamp is equivalent to a euglycemic clamp. Diabetic subjects were taken off of antidiabetic medication for 1 week before each study, and the glucose clamp was performed under isoglycemic conditions to avoid difficulties in interpretation of glucose clamp data that are acquired at levels of glycemia acutely different from fasting levels.

QUICKI

Sensitivity analyses of an initial subset of data (40%) from glucose clamp studies and the first 20 min of the FSIVGTT revealed that fasting steady state values of insulin and glucose contain sufficient information to accurately assess insulin sensitivity. We only explored the first 20 min of the FSIVGTT data because the insulin infusion initiated at 20 min would necessitate the development of a test complicated by iv infusion of insulin. After the QUICKI formula was derived from the initial subset of subjects, we then analyzed our entire study population. Similar to our results from glucose clamp studies (and in contrast to minimal model results), insulin sensitivity as assessed by QUICKI was highest in the nonobese group, intermediate in the obese group, and lowest in the diabetic group. More importantly, the overall correlation between QUICKI and SI_{Clamp} was significantly better than that obtained between SI_{MM} and SI_{Clamp}. In addition, the linear regression analysis of the subgroups corresponded more closely to the overall regression line when comparing QUICKI and SI_{Clamp}. Taken together with the fact that the overall correlation between QUICKI and SI_{Clamp} was also better than the correlation between QUICKI and SI_{MM}, our results suggest that QUICKI contains additional independent information about insulin sensitivity that is not captured by the minimal model approach. Furthermore, QUICKI provides a reproducible and robust estimate of insulin sensitivity, because equally strong correlations with SI_{Clamp} were obtained when fasting data from either the glucose clamp or FSIVGTT studies were used to calculate QUICKI. In addition, QUICKI derived from the average results of two fasting blood samples (over 10 min) was similar to QUICKI calculated from a single sample. Finally, the good correlation between QUICKI and SI_{Clamp} obtained from a

completely independent dataset acquired at a different institution provides further validation of the reliability of QUICKI.

Interestingly, when we performed subgroup comparisons between QUICKI and SI_{Clamp}, the correlations for the obese and diabetic subjects ($r = 0.89$ and 0.7, respectively) were similar to the overall correlation. However, the correlation coefficient for the nonobese subgroup was 0.49, and the greatest variability in the correlation between QUICKI and SI_{Clamp} was observed among the most insulin-sensitive subjects. There are several potential explanations for the lower correlation we observed within the nonobese subgroup. The most likely explanation for this finding is that variability in insulin determinations due to limitations in assay sensitivity causes larger percentage of errors in QUICKI when insulin levels are lowest (typical of the most insulin-sensitive subjects). Alternatively, periodic oscillations in insulin secretion (both ultradian and 10- to 15-min periods) have been reported in healthy subjects and may also contribute to the weaker correlation in this subgroup (21, 22). Interestingly, these oscillations diminish with impaired glucose tolerance and diabetes (23, 24). Therefore, in our nonobese subjects there may be a sampling error that results in aliasing of the data. However, this effect is unlikely to be occurring in our studies, because fasting samples were obtained at the same time in the morning for each subject, and calculating QUICKI from the average of several blood samples (instead of a single sample) did not significantly affect our correlations. Another possible explanation for the lower correlation between QUICKI and SI_{Clamp} in the nonobese subgroup is that the insulin infusion rate used in our glucose clamp studies was inappropriately high for individuals who are very insulin sensitive. Nevertheless, as discussed above, the good correlation between SI_{Clamp} derived from high and low insulin infusion rates suggests that our choice of high insulin infusion rate did not introduce significant error into SI_{Clamp} estimates in nonobese subjects. However, it is possible that comparison of QUICKI with clamp data obtained with low insulin infusion rates has additional variability, because hepatic glucose production may not be completely suppressed under these conditions.

Previous studies have suggested that fasting insulin *per se* may provide a reasonable index of insulin sensitivity that has positive predictive power with respect to the development of diseases associated with insulin resistance, such as obesity, hypertension, and diabetes (25–30). However, in diabetes, where fasting hyperglycemia is accompanied by inadequate insulin secretion, this relationship may not be maintained. To account for this, the so-called HOMA approach uses a mathematical model to obtain an insulin sensitivity index that is defined as the product of the fasting plasma insulin and blood glucose values divided by a constant (19). Several recent studies have demonstrated that the HOMA approach to estimating insulin sensitivity is useful in large epidemiological studies (28, 31). Interestingly, our novel index, QUICKI, is similar to HOMA, except that QUICKI also transforms the data by taking both the logarithm and the reciprocal of the glucose-insulin product. One rational for these transformations is the fact that the distribution of fasting insulin values is skewed. Thus, transformation of these data might be predicted to generate a better fit to glucose clamp measurements of insulin sensitivity. As expected, given the similarities between QUICKI and HOMA, the two methods correlate well. Nevertheless, the correlation between QUICKI and SI_{Clamp} is significantly better than the correlation between HOMA and SI_{Clamp}. Furthermore, it is clear that HOMA is not linear over wide ranges of insulin sensitivity, because the slopes of the linear regression lines for each subgroup change and generally correlate with the insulin sensitivity of each subgroup. From inspection of Fig. 6, one might predict that the relationship between HOMA and QUICKI would be described by log transformation. Indeed, log [HOMA] correlates very highly with QUICKI. This suggests that transformation of the data is beneficial for estimating insulin sensitivity and that QUICKI may be a more accurate index of insulin sensitivity than HOMA across a broad range of insulin sensitivities.

Relative merits of QUICKI

Of the three alternatives to the glucose clamp method for estimating insulin sensitivity *in vivo* that we examined in this study, QUICKI had the best overall linear correlation with the gold standard clamp measurement. In contrast to the multiple frequent blood samples and the lengthy time course required for both the glucose clamp and the minimal model approach, QUICKI can be obtained from a fasting blood sample. In addition, the ability to calculate QUICKI does not depend on a robust insulin secretory capacity, and we were able to use this method to estimate insulin sensitivity for all of our diabetic subjects (as opposed to the minimal model approach). Furthermore, in our study population, QUICKI was more accurate than either SI_{MM} or HOMA and displayed excellent reproducibility. Potential limitations to QUICKI include difficulty in applying it to subjects with type 1 diabetes who lack endogenous insulin secretion. In addition, we were unable to determine whether QUICKI is applicable to subjects with severe diabetes who could not be safely taken off of their antidiabetic medications. Nevertheless, it is also problematic to determine insulin sensitivity in subjects with type 1 diabetes and uncontrolled type 2 diabetes using other methods. Furthermore, the determination of relative insulin sensitivity and resistance in these types of subjects may be of less interest in large epidemiological studies. As QUICKI was derived from an initial subset of subjects (40%) that we then applied to our entire study population, it is possible that the correlation between QUICKI and SI_{Clamp} obtained in future studies may by slightly less than that obtained here. However, in analyzing an independent dataset, we observed very similar correlations between QUICKI and SI_{Clamp}, strongly suggesting that QUICKI is a robust index of insulin sensitivity.

We conclude that fasting glucose and insulin levels contain sufficient information to accurately assess insulin sensitivity *in vivo* over a wide range in a diverse population. QUICKI is a novel, simple, accurate, and reproducible method for determining insulin sensitivity in humans that may be a useful tool in large epidemiological investigations that study the role of insulin resistance in the pathophysiology of important public health problems such as obesity, cardiovascular diseases, and diabetes.

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