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Modified Quantitative Insulin Sensitivity Check Index Is Better Correlated to Hyperinsulinemic Glucose Clamp than Other Fasting-Based Index of Insulin Sensitivity in Different Insulin-Resistant States

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Fasting-based index estimates of insulin sensitivity were compared with euglycemic hyperinsulinemic clamp (IS clamp) measurements in 148 subjects: normal controls (n = 46), and obese (n = 12), polycystic ovary syndrome (n = 16), first-degree relatives of type 2 diabetic (n = 17), impaired glucose tolerance (n = 28), and type 2 diabetic (n = 29) patients. The fasting-based indexes tested included log homeostasis model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI), the revised QUICKI, and a new revised QUICKI using fasting plasma glycerol.

In the population studied, at 40 mU/m^2·min (n = 30) revised QUICKI (r = 0.86; $P < 0.0001$) and QUICKI-glycerol (r = 0.87; $P < 0.0001$) gave higher correlations with the IS clamp than QUICKI and log HOMA (r = 0.78 and r = −0.78; $P < 0.001$). For subjects tested at 75 mU/m^2·min (n = 118), comparable correlations were found for all indexes (r > 0.80; $P < 0.0001$). When studied in subgroups, revised QUICKI and QUICKI-glycerol give significantly higher correlations with the IS clamp than other indexes for lean control subjects studied at 40mU/m^2·min and impaired glucose tolerance subjects.

We confirmed, in a large patient population with a wide range of insulin sensitivities, that no single test is superior in all groups of patients. However, QUICKI and revised QUICKI are good indexes that offer correlations similar to or higher than values obtained with log HOMA. Such indexes are simple tools to estimate insulin sensitivity appropriate for epidemiological studies. (*J Clin Endocrinol Metab* 88: 4917–4923, 2003)

INSULIN RESISTANCE IS a key component of several diseases, including type 2 diabetes, obesity, hypertension, dyslipidemia, and cardiovascular disorders (1). Several methods are available to assess insulin sensitivity in humans, the "gold standard" being the euglycemic hyperinsulinemic clamp (IS clamp) because it directly measures the insulin action on glucose utilization under steady-state conditions (2). However, this technique is laborious and only applicable to a small number of subjects. Recently, Katz *et al.* (3) proposed a new, accurate index to assess insulin sensitivity in humans. This index, called "QUICKI" for the quantitative insulin sensitivity check index, is defined from fasting plasma glucose and insulin as 1/[log (fasting insulin) + log (fasting glucose)].

It has been shown that QUICKI is an accurate index of insulin sensitivity (3, 4), better correlated to the gold standard IS clamp than other indexes, such as the minimal model index or homeostasis model assessment (HOMA) (5, 6). However, QUICKI is less correlated to the glucose clamp in nonobese, nondiabetic control subjects than in obese and type 2 diabetic patients (3). More recently, Perseghin *et al.* (7), by incorporating fasting plasma free fatty acid (FFA) concentration into QUICKI, improved its correlation to the IS clamp and its discriminatory power in cases of mild insulin-resistant states. However, it is not known whether this revised QUICKI improves its association in insulin-resistance states, such as obesity, impaired glucose tolerance (IGT), polycystic ovary syndrome (PCOS), and type 2 diabetes mellitus. Because FFA can be reesterified or excreted in adipose tissue, whereas glycerol is always excreted, the latter could give more precise information than FFA on lipolysis.

The aims of this study were to: 1) determine whether the incorporation of fasting plasma FFA concentration into QUICKI could improve its association with the glucose clamp in several nondiabetic, insulin-resistant states; and 2) assess whether plasma glycerol could give additional information when included in the revised QUICKI formula.

Abbreviations: BMI, Body mass index; FFA, free fatty acid(s); GIR, glucose infusion rate; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IS clamp, euglycemic hyperinsulinemic clamp; PCOS, polycystic ovary syndrome; QUICKI, quantitative insulin sensitivity check index.

Subjects and Methods

Subjects

The population was selected from studies conducted between 1995 and 2002. We extracted data on all subjects (ages, 18–70 yr) investigated by the standardized IS clamp (insulin infusion at 40 or 75 mU/m^2·min)

who had identical quantifications of plasma glucose, insulin, FFA, and glycerol. A total of 148 of 188 subjects met these requirements. This population included: 46 controls (18 studied with 40 mU/m^2·min insulin infusion, and 28 with 75 mU/m^2·min), 12 obese (40 mU/m^2·min), 16 females with PCOS (75 mU/m^2·min), 17 first-degree relatives of type 2 diabetic patients (75 mU/m^2·min), 28 IGT (75 mU/m^2·min), and 29 type 2 diabetic patients (75 mU/m^2·min).

Clinical and biological characteristics of these patients are described in Tables 1 and 2. All patients had a stable weight in the 3 months preceding the clamp. None presented major health problems such as liver anomalies, pulmonary disease, renal insufficiency, coronary artery disease, heart failure, or peripheral vascular disease. The controls were defined by normal weight [body mass index (BMI), 18–25 kg/m^2], no first- and second-degree family history of obesity or diabetes, and normal glucose tolerance. Obese patients had normal glucose tolerance and a BMI over 30 kg/m^2. PCOS patients had BMI lower than 30 kg/m^2 with severe oligomenorrhea, increased plasma concentration of at least 1 androgen [SHBG, bound testosterone > 5.5 ng/dl, and/or androstenedione > 230 ng/dl with ultrasonography revealing at least 10 small ovarian cysts/follicles (2–8 mm diameter)]. First-degree relatives had to have at least 1 parent with type 2 diabetes and normal glucose tolerance. IGT was defined during a 75-g oral glucose test using 1997 American Diabetes Association criteria (8). Type 2 diabetic patients needed to have a known diagnosis for more than 9 months and were studied after 4 d of oral hypoglycemic agent withdrawal if fasting blood glucose did not exceed 17.0 mmol/liter.

We chose to divide the subjects by clinical characteristics rather than with a *post hoc* definition of insulin sensitivity based on clamp outcome. Although this results in some overlap in insulin sensitivity across groups, it provides a better match with the prospective approach because such clinical characteristics are the main criteria for inclusion in all studies. All subjects gave their written consent after being informed of the nature and purpose of the study, including its possible risks. The experimental protocol, approved by the ethics committee of Hospices Civils de Lyon and Assistance Publique – Hôpitaux de Paris, was performed according to the Helsinki Declaration and French legislation for research on human subjects (Huriet law).

TABLE 1. Clinical and biological characteristics of the subjects studied with insulin infusion of 40 mU/m^2·min

	Control (40 mU/m^2·min)	Obese (40 mU/m^2·min)
N	18	12
Age (yr)	27.7 ± 1.8	35.2 ± 3.5
BMI (kg/m^2)	22.6 ± 0.36	34.0 ± 1.7[a]
Sex ratio (M/F)	10/8	5/7
Plasma glucose (mmol/liter)	4.8 ± 0.1	5.1 ± 0.2
Plasma insulin (μU/ml)	7.0 ± 0.5	14.1 ± 1.8[a]
Plasma FFA (μmol/liter)	498 ± 57	534 ± 60
Plasma glycerol (μmol/liter)	72.3 ± 7.9	81.2 ± 11.2

Comparisons *vs.* control were made using nonparametric Mann-Whitney *U* test.
[a] $P < 0.001$.

Study design

Except for the insulin infusion rate, the design of the clamp studies was uniform. Four days before the clamp, the subjects were instructed to avoid exercise. After an overnight (10-h) fast, all patients underwent a 3-h IS clamp (9). An antecubital vein of one arm was cannulated for infusion of 20% dextrose, potassium phosphate, and insulin (Actrapid, Novo-Nordisk, Copenhagen, Denmark). In diabetic subjects and subjects studied at 40 mU/m^2·min, D2-glucose ([6,6-^{2}H2]glucose; Euristop, St-Aubain, France) was used to measure the glucose turnover rate (10). The other arm was cannulated for sampling of arterialized blood. Insulin, D2-glucose, and 20% dextrose were delivered by calibrated syringe pumps (IVAC, Alaris, P7000; Hampshire, UK). Blood was drawn every 10 min during the last 30 min of the basal period for measurement of plasma glucose, insulin, glycerol, and FFA. After the basal period, an insulin infusion was started at the rate of 40 or 75 mU/m^2·min for 180 min. Plasma glucose was measured every 10 min with a glucose analyzer (Beckman Instruments, Fullerton, CA) to adapt dextrose infusion. For normo-glycemic subjects, plasma glucose was clamped between 4.5 and 5.5 mmol/liter. For type 2 diabetic and IGT patients, a decline to 5.0 ± 0.5 mmol/liter was allowed, this value being maintained by using a variable infusion rate of 20% dextrose. During the last 40 min of the clamp, insulin and isotopic enrichment (type 2 diabetics and patients studied at 40 mU/m^2·min) were again measured to obtain values in a steady-state situation.

Laboratory analyses

Plasma glucose was quantified by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and plasma insulin by RIA (Ins Irma, Kip 1251, MDS Nordion, Orsay, France). FFA were assessed by colorimetry (Wako Chemical, Neuus, Germany). Plasma glycerol was measured by the enzymatic method (11). Plasma isotopic enrichment of D2-glucose was quantified by gas chromatography-mass spectrometry (MSD 5971; Hewlett-Packard, Palo Alto, CA) as described previously (9).

Calculations

For the fasting-based index and IS clamp, insulin sensitivity was calculated from the means of four values obtained over a 30-min period. The mean glucose infusion rate (GIR) in the last 30 min of insulin infusion was used to determine the IS clamp as follows: $IS_{(clamp)} = GIR_{ss}/G_{ss} \times \Delta I_{ss,}$ where GIR_{ss} is the steady-state GIR (milligrams/kilogram × minutes), G_{ss} is the steady-state blood glucose concentration (milligrams per deciliter), and ΔI_{ss} is the difference between the steady-state and basal insulin concentration (microunits per milliliter) (7).

QUICKI was calculated as described previously (3): QUICKI = $1/[\log(G_b) + \log(I_b)]$ where G_b is fasting plasma glucose (milligrams per deciliter), and I_b is fasting plasma insulin (microunits per milliliter). Revised QUICKI was calculated as described by Perseghin *et al.* (7): revised QUICKI = $1/[\log(G_b) + \log(I_b) + \log(FFA_b)]$, where FFA_b is

TABLE 2. Clinical and biological characteristics of the subjects studied with insulin infusion of 75 mU/m^2·min

Population (insulin infusion)	Control (75 mU/m^2·min)	IGT (75 mU/m^2·min)	First-degree relatives (75 mU/m^2·min)	PCOS (75 mU/m^2·min)	Type 2 diabetic patients (75 mU/m^2·min)	*P* (comparison between groups)
N	28	28	17	16	29	
Age (yr)	35.3 ± 2.7	54.6 ± 1.3[a]	28.9 ± 1.6	22.8 ± 1.1[b]	53.2 ± 1.42[a]	<0.0001
BMI (kg/m^2)	22.6 ± 0.4	31.9 ± 0.9[a]	27.5 ± 1.6[b]	23.7 ± 0.8	30.6 ± 0.7[a]	<0.0001
Sex ratio (M/F)	7/21	13/15	3/14	0/16	14/15	
Plasma glucose (mmol/liter)	4.7 ± 0.1	6.5 ± 0.15[a]	4.9 ± 0.1	4.6 ± 0.1	11.8 ± 0.6[a]	<0.0001
Plasma insulin (μU/ml)	5.5 ± 0.5	9.71 ± 1.1[b]	10.6 ± 1.5[a]	9.5 ± 1.6	10.8 ± 1.1[a]	<0.0001
Plasma FFA (μmol/liter)	497 ± 40	618 ± 27	534 ± 35	535 ± 41	680 ± 49[b]	0.008
Plasma glycerol (μmol/liter)	64.6 ± 7.0	NA	73.9 ± 6.2	NA	71.4 ± 7.5	0.80

Comparisons *vs.* control were made using nonparametric Mann-Whitney *U* test. Comparisons between groups were made using nonparametric Kruskall-Wallis test. NA, Not available.
[a] $P < 0.001$.
[b] $P < 0.05$.

fasting plasma FFA (millimoles per liter). To explore whether glycerol could add important information, QUICKI-glycerol was calculated in a similar fashion as revised QUICKI: QUICKI-glycerol = $1/[\log(G_b) + \log(I_b) + \log(\text{Glycerol}_b)]$ where Glycerol_b is fasting plasma glycerol (micromoles per liter).

HOMA was calculated according to the formula of Matthews *et al.* (6), *i.e.* HOMA: [Fasting insulin (microunits per milliliter) × Fasting glucose (millimoles per liter)]/22.5.

Statistical analysis

All of the results are presented as means ± SE. For clamp studies at 40 mU/m²·min insulin infusion rate, differences between obese and control subjects were determined by the Mann-Whitney *U* test. For clamp studies at 75 mU/m²·min insulin infusion rate, differences between groups were determined by the Kruskall-Wallis test followed by the Mann-Whitney *U* test for comparison between each group and the control group. Correlations were calculated by Spearman's rank correlation test. The threshold for significance was set at $P = 0.05$. Comparison between correlations has been made using the method reported by Zar (12).

Results

Subjects

We studied 148 subjects divided into different subgroups according their pathology, *i.e.* obesity, PCOS, IGT, first-degree relatives of type 2 diabetics, and type 2 diabetic patients. Characteristics of the subjects are summarized in Tables 1 and 2. In the insulin-stimulated condition (40 mU/m²·min), steady-state plasma glucose was 5.1 ± 0.1 mmol/liter, whereas plasma insulin was 89.0 ± 3.8 μU/ml with no difference between control and obese subjects. At 75 mU/m²·min, steady-state plasma glucose was 4.8 ± 0.1 mmol/liter, and plasma insulin was 171.8 ± 4.0 μU/ml with no significant difference between groups (data not shown).

TABLE 3. Insulin sensitivity measured with euglycemic hyperinsulinemic clamp (IS clamp) and fasting based estimates of insulin sensitivity for subjects studied with insulin infusion of 40 mU/m²·min

	Control (40 mU/m²·min)	Obese (40 mU/m²·min)
N	18	12
SI	14.4 ± 1.2	6.63 ± 0.8[a]
QUICKI	0.364 ± 0.005	0.326 ± 0.006[a]
QUICKI-FFA	0.418 ± 0.008	0.364 ± 0.01[a]
QUICKI-glycerol	0.219 ± 0.002	0.203 ± 0.004[a]
Log HOMA	0.150 ± 0.042	0.472 ± 0.056[a]

Comparison *vs.* control were made using nonparametric Mann-Whitney *U* test.
[a] $P < 0.001$.

Indices of insulin sensitivity

IS clamp and fasting-based estimates of insulin sensitivity are given in Tables 3 and 4. As expected, a wide range of insulin resistance was observed. Control subjects were more insulin-sensitive, followed by normoglycemic obese, first-degree relatives, PCOS patients, and IGT subjects, whereas obese type 2 diabetic patients were the most insulin-resistant.

When we analyzed control and obese subjects together (n = 30) at 40 mU/m²·min insulin infusion, we found a higher correlation between IS clamp and either revised QUICKI (r = 0.86; $P < 0.0001$) or QUICKI-glycerol (r = 0.87; $P < 0.0001$) than both QUICKI and log HOMA (r = 0.78, $P < 0.0001$; and r = −0.78, $P < 0.0001$, respectively) (Fig. 1, C and D). However, this difference did not reach a statistically significant level. For subjects studied at 75 mU/m²·min insulin infusion rate (n = 118), we obtained a comparable correlation between revised QUICKI (r = 0.83; $P < 0.0001$) and both QUICKI and log HOMA (r = 0.81, $P < 0.0001$; and r = −0.81, $P < 0.0001$, respectively) (Fig. 1, A and B).

Correlations between IS clamp and various fasting-based insulin resistance indexes in the different subgroups are shown in Table 5.

In the insulin-resistant groups, revised-QUICKI gave a comparable or higher correlation with the IS clamp than the other indexes. In IGT and PCOS patients, two groups in which revised QUICKI has not yet been investigated, revised QUICKI showed the best correlation with the IS clamp, this difference being significant for IGT patients ($P < 0.01$). However, in type 2 diabetic patients, QUICKI and log HOMA appeared as good as revised QUICKI in estimating insulin resistance. QUICKI-glycerol was studied in a smaller group of patients and gave correlations similar to revised-QUICKI. Correlations tended to be lower in the control group than in different groups of insulin-resistant subjects. However, it was significantly higher for control subjects studied at the 40 mU/m²·min insulin infusion rate when either plasma FFA or plasma glycerol was included in the insulin sensitivity index calculation ($P < 0.05$ and 0.001, respectively) (Table 5).

Discussion

We evaluated various estimates of insulin sensitivity based on fasting plasma glucose, insulin, FFA, or glycerol

TABLE 4. Insulin sensitivity measured with euglycemic hyperinsulinemic clamp (IS clamp) and fasting based estimates of insulin sensitivity for subjects studied with insulin infusion of 75 mU/m²·min

Population (insulin infusion)	Control (75 mU/m²·min)	IGT (75 mU/m²·min)	First-degree relatives (75 mU/m²·min)	PCOS (75 mU/m²·min)	Type 2 diabetic patients (75 mU/m²·min)	*P* (comparison between groups)
N	28	28	17	16	29	
SI	8.5 ± 0.6	4.0 ± 0.4[a]	6.4 ± 0.8[b]	5.5 ± 0.6[b]	2.8 ± 0.4[a]	<0.0001
QUICKI	0.384 ± 0.006	0.338 ± 0.006[a]	0.346 ± 0.006[a]	0.353 ± 0.024	0.302 ± 0.004[a]	<0.0001
QUICKI-FFA	0.448 ± 0.013	0.367 ± 0.008[a]	0.385 ± 0.009[a]	0.395 ± 0.008	0.323 ± 0.007[a]	<0.0001
QUICKI-glycerol	0.234 ± 0.006	NA	0.211 ± 0.003[b]	NA	0.192 ± 0.004[a]	0.0002
Log HOMA	0.014 ± 0.042	0.377 ± 0.053[a]	0.301 ± 0.053[a]	0.237 ± 0.053	0.722 ± 0.043[a]	<0.0001

Comparisons *vs.* control were made using nonparametric Mann-Whitney *U* test. Comparisons between groups were made using nonparametric Kruskall-Wallis test. N/A, Not available.
[a] $P < 0.001$.
[b] $P < 0.05$.

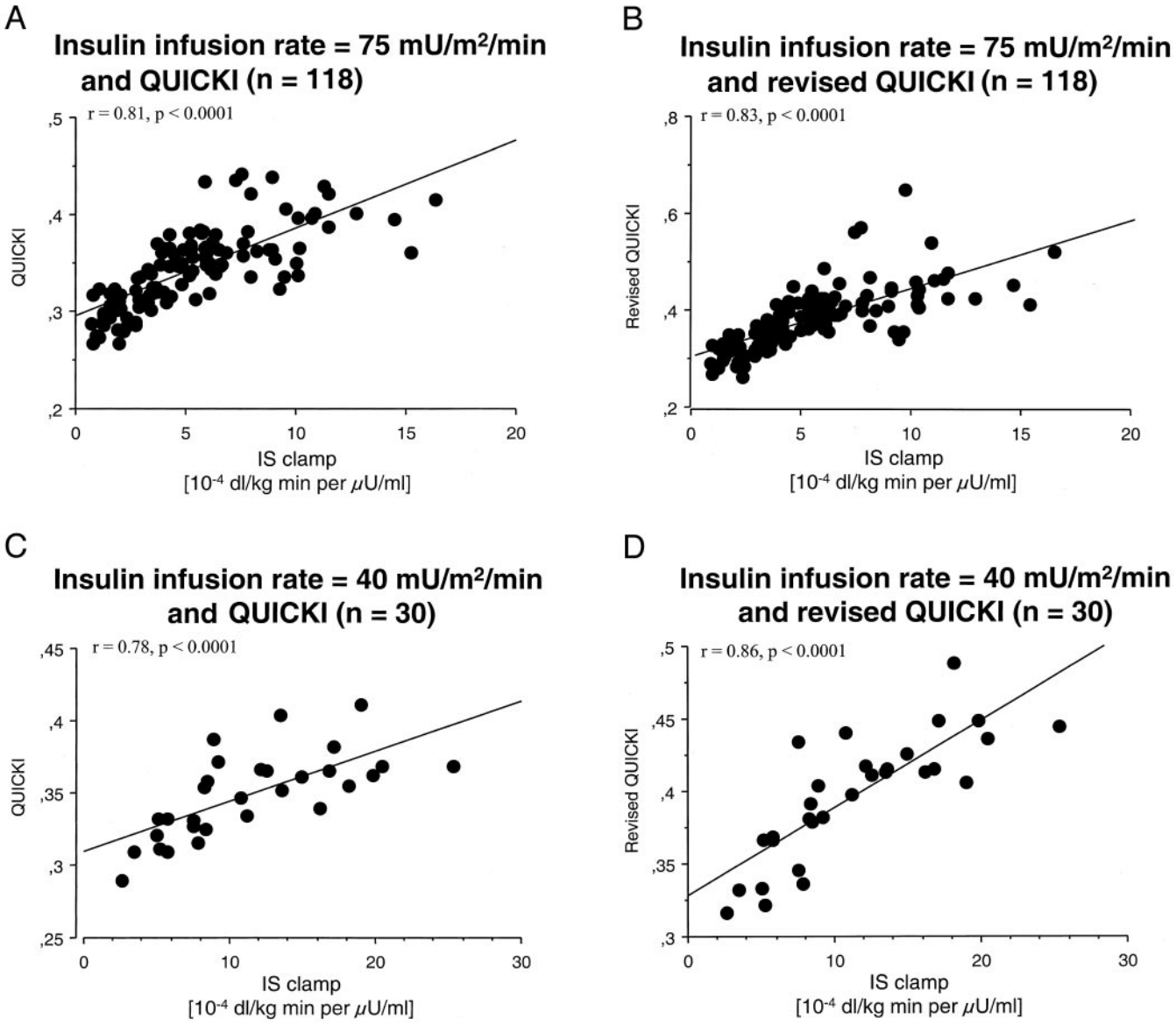

FIG. 1. Correlation between IS clamp and QUICKI (A and C) and revised QUICKI (B and D). Values from A and B (n = 128) were obtained with insulin infusion at 75 mU/m²·min, and values from C and D (n = 30) were obtained with insulin infusion at 40 mU/m²·min.

and compared them with values obtained during IS clamp in a large population with a wide range of insulin sensitivities. Our results reaffirmed the usefulness of indexes such as QUICKI or revised QUICKI, especially in the insulin-resistant state. We also confirmed that adding FFA in the QUICKI calculation can significantly improve correlations with values obtained during the IS clamp for control subjects, and we extended this observation to IGT states. However, in type 2 diabetic patients, various indexes gave comparable results. Interestingly, our findings indicated that fasting plasma glycerol generated data close to those obtained when FFA was incorporated in the formula.

Fasting-based indexes like HOMA, QUICKI, and revised QUICKI offer important advantages in estimating insulin sensitivity. They generate good and linear correlations with direct euglycemic hyperinsulinemic measurement of insulin sensitivity in different populations (3, 7, 13) as well as with other estimates of insulin sensitivity (14–17). They are obtained from a few fasting blood samples and are thus suitable for large epidemiological studies. They do not depend on robust insulin secretory capacity, allowing the estimation of insulin sensitivity in type 2 diabetic patients in whom the use of other methods, such as the minimal model approach, can be difficult. Finally, simple indexes have been shown to differentiate insulin sensitivity between groups and prospectively track insulin sensitivity modifications in different but not all populations and pathophysiological situations (4, 7, 13, 17–29). Low insulin sensitivity estimated by QUICKI is also independently associated with carotid atherosclerosis (30). Limitations include mainly non-steady-state situations, such as hypocaloric diets, uncontrolled type 2 diabetes, and physical training (17, 31, 32).

The confirmation of a higher correlation of revised QUICKI than QUICKI with clamp measurement of insulin

TABLE 5. Correlation between insulin sensitivity measured with euglycemic hyperinsulinemic clamp (IS clamp) and fasting based estimates of insulin sensitivity in various subgroups

	Control 40	Control 75	Obese 40	IGT 75	First-degree relatives 75	POCS 75	Diabetic 75
QUICKI *vs.* IS clamp	n = 18	n = 28	n = 12	n = 28	n = 17	n = 16	n = 29
	r = 0.464	r = 0.406	r = 0.797	r = 0.655	r = 0.718	r = 0.579	r = 0.754
	$P = 0.055$	$P = 0.035$	$P = 0.0082$	$P = 0.0007$	$P = 0.0041$	$P = 0.025$	$P < 0.0001$
QUICKI-FFA *vs.* IS clamp	n = 18	n = 28	n = 12	n = 28	n = 17	n = 16	n = 29
	r = 0.651	r = 0.374	r = 0.881	r = 0.802	r = 0.686	r = 0.671	r = 0.767
	$P = 0.0073$[a]	$P = 0.052$	$P = 0.0035$	$p < 0.0001$[b]	$P = 0.006$	$P = 0.0094$	$P < 0.0001$
QUICKI-glycerol *vs.* IS clamp	n = 18	n = 9	n = 12		n = 17		n = 12
	r = 0.818	r = 0.367	r = 0.678	NA	r = 0.718	NA	r = 0.615
	$P = 0.0007$[a]	$P = 0.30$	$P = 0.024$		$P = 0.0041$		$P = 0.041$
Log HOMA *vs.* IS clamp	n = 18	n = 28	n = 12	n = 28	n = 17	n = 16	n = 29
	r = −0.462	r = −0.406	r = −0.790	r = −0.655	r = −0.716	r = −0.579	r = −0.754
	$P = 0.056$	$P = 0.035$	$P = 0.0088$	$P = 0.0007$	$P = 0.0041$	$P = 0.025$	$P < 0.0001$

NA, Not available.

[a] The higher correlation obtained QUICKI-FFA and QUICKI-glycerol for control subjects studied with insulin infusion at 40 mU/m^2·min is significantly higher than all other correlation with IS clamp ($P < 0.05$ and $P = 0.001$, respectively).

[b] The higher correlation obtained QUICKI-FFA for IGT subjects is significantly higher than all other correlation with IS clamp ($P < 0.01$).

resistance in some groups, and the similar results obtained with QUICKI-glycerol despite a smaller number of subjects, reinforce the hypothesis of Perseghin *et al.* (7) that markers of lipolysis − besides fasting plasma glucose and insulin − can add significant information to estimate insulin sensitivity.

Several reasons can explain the usefulness of incorporating FFA into the QUICKI formula: 1) Lipolysis is more sensitive to insulin than glucose utilization; thus, increased fasting FFA concentrations could reflect insulin resistance earlier than glycemia (33). 2) An experimental increment of plasma FFA concentrations in healthy patients induces insulin resistance (34). It is estimated that insulin sensitivity of lipolysis can explain about 10% of the variation in insulin sensitivity of glucose disposal in normal subjects with relationship between the two processes (33). 3) In insulin-resistant subjects, impaired regulation of lipolysis has been well-established (35).

Like FFA, plasma glycerol reflects lipolysis, which is controlled for the most part by plasma insulin. Because FFA can be reesterified or excreted, whereas glycerol is always excreted, plasma glycerol could give interesting information (36). The availability of glycerol in a fraction of the population limits the conclusion that can be drawn; however, the results obtained with QUICKI-glycerol appear to be close to those obtained with revised-QUICKI (Table 5). Thus, the eventual interest in this index awaits studies in larger populations.

The benefit from adding a marker of lipolysis to the QUICKI formula is not constant because we noted no improvement of correlations for type 2 diabetics, obese subjects, and first-degree relatives of diabetic patients. In type 2 diabetic patients, it is possible that the differences in plasma FFA concentrations become negligible, compared with the high variation of glycemia and insulinemia, and are thus, insufficient to improve QUICKI accuracy. The inverse situation could prevail in control subjects where the small variation observed in a lipolysis marker added to the formula could improve the sensitivity of QUICKI. In obese subjects and first-degree relatives, it can be speculated that FFA interindividual variation is lower than that of insulin, which could explain the lack of improvement by adding FFA into QUICKI.

Formulae including the lipolysis marker should, however, be used with caution in situations where FFA levels are affected by interventions. We have recently reported that after a very low-calorie diet, in which FFA level reflected mainly lipolysis induced by diet rather than resistance to the antilipolytic effect of insulin, revised QUICKI gave false interpretations of insulin-sensitivity modifications (31).

For lean control subjects, there is a less robust correlation between QUICKI and the IS clamp than for insulin-resistant groups, whatever the insulin infusion rate studied. Other indexes confirm a lower correlation between fasting-based index estimation and clamp measurement of insulin resistance in control subjects (Table 5). It has already been suggested that QUICKI and HOMA less accurately reflect insulin sensitivity in insulin-sensitive populations than in more insulin-resistant groups (3, 14, 18). Our data also confirm that higher correlations are obtained between QUICKI and euglycemic clamp in normal subjects when they are studied at a low infusion rate (40 mU/m^2·min) but not at higher rates (18), and we extend this notion to revised QUICKI. It could be hypothesized that measurement of insulin resistance with a high level of insulin (75 mU/m^2·min) does not explore the same component of insulin resistance as clamps using lower doses (40 mU/m^2·min). Fasting-based indexes could be closer to the IS clamp measured with a lower insulin infusion rate (37). Although insulin infusion at 40 mU/m^2·min is high to explore sensitivity of lipolysis to insulin, it could still incorporate some information that is not present with higher doses of insulin. This is supported by the fact that the addition of lipolysis markers, which is more sensitive to the effect of insulin, in the formula can improve the sensitivity of QUICKI in control subjects.

On the other hand, lower correlations in normal subjects could be secondary to the greater variability of insulin assay (including ultrasensitive assays) in the lower normal range associated with known physiological pulsatility secretion and the short-term serum half-life of insulin (18, 38). In control subjects, fasting glucose and insulin are both within a narrow range, which makes it difficult for indexes solely

based on these variables to span with accuracy the wide spectrum of insulin sensitivity present in normal individuals. The absence of or lower correlation between the IS clamp and QUICKI in lean control groups could also be due to population characteristics: BMI inclusion criteria were strictly limited to the normal range, whereas previous works also included overweight (25–30 kg/m^2) and underweight (<18 kg/m^2) subjects. Moreover, our control group did not include any first- or second-degree diabetic relatives; and, finally, some control subjects included in previous studies were already quite insulin-resistant (mean glucose infusion rate, 4.85 ± 0.25 mg/kg·min) compared with the usual values in normal populations (7, 14, 18). The presence of a good correlation in global populations, with significantly lower correlation in some subgroups (*i.e.* lean controls), indicates that fasting-based indexes of insulin sensitivity, despite their evident usefulness, should be used with caution in normal populations because an insulin-resistant subset could systematically affect correlation with other measures in a larger population (18).

In conclusion, we confirmed in a large group of patients across a broad range of insulin sensitivities that no single test is highly superior in all groups of patients, but QUICKI and revised QUICKI are good indexes that offer correlations similar to or higher than values obtained with log HOMA. We confirmed the validity and usefulness of these indexes in PCOS and IGT populations, two groups in which insulin resistance is a central mechanism of pathogenesis disease. When groups are studied separately, revised QUICKI or QUICKI-glycerol appears better related to the IS clamp than other indexes if insulin sensitivity is measured with insulin infusion at 40 mU/m^2·min for control subjects and IGT subjects with insulin infusion at 75 mU/m^2·min. The results with revised QUICKI and a formula including glycerol are interesting because they add information about the insulin action on lipolysis, which is related to the insulin action on glucose metabolism. Promising data obtained with index incorporating information on lipolysis should be confirmed in a larger population, especially in normal, sensitive subjects in which fasting-based indexes give lower correlations. Fasting-based indexes are simple tools appropriate for epidemiological studies.

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