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Incorporation of the Fasting Plasma FFA Concentration into QUICKI Improves Its Association with Insulin Sensitivity in Nonobese Individuals

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Insulin resistance plays a major role in the pathophysiology of diabetes and is associated with obesity and cardiovascular disease. Excellent methods exist for the assessment of insulin sensitivity in the laboratory setting, such as the glucose clamp. However, these methods are not suitable for large population studies, and, thus, surrogate estimates of insulin sensitivity based on measurements in a single blood sample have been developed. Recently an index based on the logarithm and the reciprocal of the insulin-glucose product (QUICKI) has been proposed. QUICKI correlated with insulin sensitivity across the entire spectrum of glucose tolerance, but its performance was less satisfactory in normal subjects. Aim of this study was to ascertain whether the inclusion of fasting plasma free fatty acids concentration into QUICKI improves its association with insulin sensitivity in nonobese subjects. To test this hypothesis, we performed a euglycemic hyperinsulinemic clamp [40 mU/(m^2·min)] in 57 young, healthy, nonobese individuals with (n = 17) or without (n = 40) first-degree relatives affected by type 2 diabetes (the former group being an *in vivo* model of mild insulin resistance). We then compared the clamp-based index of insulin sensitivity with both QUICKI and a revised QUICKI, the latter index including the contribution of fasting free fatty acid concentration as well. The revised QUICKI considerably improved the relationship with the clamp-based index of insulin sensitivity (r = 0.51, $P < 0.0001$) with respect to QUICKI (r = 0.27, $P < 0.05$). In addition, the revised QUICKI revealed a reduction of insulin sensitivity in the offspring of type 2 diabetes (10%; $P < 0.006$) that QUICKI was unable to detect (3%; $P = 0.28$). In conclusion, this study suggests that the incorporation of fasting free fatty acid level into QUICKI is useful to improve its correlation with the clamp-based index of insulin sensitivity and its discriminatory power in case of mild insulin resistance. Further investigation is needed to ascertain its applicability to patients with obesity and type 2 diabetes. (*J Clin Endocrinol Metab* 86: 4776–4781, 2001)

INSULIN RESISTANCE IS a key factor involved in the pathogenesis of type 2 diabetes (1, 2). Longitudinal studies showed that insulin resistance is the stronger predictive factor of the future development of the disease (2–4). It was found to be associated with obesity, hypertension, dyslipidemias (5), and prevalent atherosclerosis (5–7), and the clustering of these metabolic disorders is now recognized as the insulin resistance syndrome (8, 9). The recognition of insulin resistance therefore has investigational and clinical relevance in the identification of subjects at high risk of developing this syndrome.

The insulin clamp technique (10) is considered the gold standard (11) for *in vivo* quantification of insulin sensitivity. A well-accepted alternative is the minimal model analysis of a frequently sampled iv glucose tolerance test (12), which is less laborious but is not as simple as required in large-scale studies.

The homeostasis model assessment index (HOMA), which is based on the product of the fasting plasma insulin and blood glucose concentrations measured in a single blood sample, has been proposed as a simple and inexpensive tool to measure insulin sensitivity (13). HOMA has been shown to be a reliable measure of *in vivo* insulin sensitivity in humans when compared with the euglycemic-hyperinsulinemic clamp technique across the entire spectrum of glucose tolerance (14).

Recently Katz *et al.* (15) showed that by taking both the logarithm and the reciprocal of the insulin-glucose product, one derives an index, denoted as Quantitative Insulin sensitivity Check Index (QUICKI), that provides a better prediction of insulin sensitivity. These authors examined nonobese, obese, and type 2 diabetic patients and found a very good agreement between QUICKI and the clamp-based index of insulin sensitivity (overall r = 0.78). In making subgroup comparisons, however, they found the lowest correlation coefficient (r = 0.49) and the greatest variability in the nonobese subgroup. This finding suggests that in such groups of individuals, QUICKI still has margins of improvement and that additional metabolic markers of insulin action—besides glucose and insulin—could be profitably taken into account to improve its association with insulin sensitivity.

The aim of this study is to determine whether incorporation of the fasting FFA concentration into QUICKI can improve the association of this index with insulin sensitivity in nonobese subjetcs. To test our hypothesis, we performed euglycemic hyperinsulinemic clamp studies in 57 young,

Abbreviations: CV, Coefficient of variation; GIR, glucose infusion rate; HOMA, homeostasis model assessment index; IR, insulin resistance; QUICKI, Quantitative Insulin sensitivity Check Index; $S_{I(clamp)}$, glucose clamp-derived index of insulin sensitivity.

healthy, nonobese individuals—with or without a first-degree relative affected by type 2 diabetes mellitus—and compared the clamp-based estimate of insulin sensitivity with both QUICKI and a revised QUICKI, the latter index including the contribution of fasting FFA concentration as well.

Materials and Methods

Subjects

Fifty-seven healthy, young, nonobese subjects were recruited at the Istituto Scientifico H San Raffaele. The main criteria for their inclusion in the study were the following: 1) age (19–45 yr); 2) white race; 3) body mass index less than 27 kg/m^2; 4) sedentary lifestyle; and 5) no history of hypertension, endocrine/metabolic disease, or cigarette smoking. Habitual physical activity was assessed using a questionnaire (16). Body weight was stable for at least 6–12 months. The anthropometric characteristics of the subjects are summarized in Table 1. Seventeen individuals resulted to have at least one parent with type 2 diabetes; meanwhile, the remaining 40 individuals had no family history of diabetes. These subjects were studied to test whether incorporation of fasting FFA concentration into QUICKI can improve its association with insulin sensitivity. An additional subgroup of 14 healthy, nonobese subjects was recruited to undergo a dose-response study at low and high insulin infusion rate aimed to test whether the antilipolytic insulin action was associated with insulin sensitivity to glucose metabolism at different circulating insulin levels. All subjects were in good health as assessed by medical history, physical examination, hematological assay, and urinalysis. Informed consent was obtained from all subjects after explanation of purposes, nature, and potential risks of the study. The protocol was approved by the Ethical Committee of the Istituto Scientifico H San Raffaele.

Experimental protocol

Subjects were instructed to consume an isocaloric diet and to abstain from exercise activity for 3 wk before the studies. Women were studied between days 3 and 8 of the menstrual cycle. Subjects were studied by means of the euglycemic-hyperinsulinemic clamp to assess insulin sensitivity after a 10-h overnight fast period. Within 2–3 d, they were also studied by means of dual-energy x-ray absorptiometry in the Department of Science, Nutrition, and Microbiology, Nutrition Section, Università degli Studi di Milano, to assess body composition.

Euglycemic-hyperinsulinemic clamp. Subjects were admitted to the Metabolic Unit of the Division of Internal Medicine I of the Istituto Scientifico H San Raffaele at 0700 h after a 10-h overnight fast. A Teflon catheter was inserted into an antecubital vein for infusions and an additional one was inserted retrogradely into a wrist vein for blood sampling. The hand was kept in a heated box (50 C) throughout the experiment to allow sampling of arterialized venous blood. Blood samples for postabsorptive plasma glucose, insulin and FFAs were performed in triplicate. Thereafter a euglycemic/hyperinsulinemic clamp was performed as previously described (17). Insulin was infused at 40 mU/[m^2·min] to reach a plasma insulin concentration of about 350 pmol/liter, and plasma glucose concentration was kept at 5 mmol/liter for 150 min by means of a variable infusion of 20% dextrose infusion. Blood samples for plasma insulin, glucose, and FFAs were drawn every 15 min throughout the study.

Body composition. Body composition, with regional three-compartment analysis (arms, trunk, and legs), was performed with a Lunar Corp.-DPX-IQ scanner (Lunar Corp., Madison, WI) as previously described (17). Fat content is expressed as kilograms of fat mass and as percent of tissues.

Dose-response study of the antilipolytic insulin action. To assess whether insulin sensitivity of lipolysis and glucose metabolism were associated, a subgroup of 14 subjects (age = 35 ± 3 yr, body mass index = 24.5 ± 1.1 kg/m^2) performed a dose-response clamp study using insulin infusion rates of 10 (low dose) and 40 (high dose) mU/(m^2·min). The low-dose insulin clamp was designed to reach appropriate (150 pmol/liter) plasma insulin levels to investigate the antilipolytic insulin action.

Analytical procedures

Plasma glucose was measured with a glucose analyzer (Beckman Coulter, Inc., Fullerton, CA) (17) and coefficient of variation (CV) was 1.7 ± 0.1% and 3.0 ± 0.4%, respectively, in the fasting and clamp conditions. Plasma insulin was measured with a microparticle enzyme immunoassay technology (18) with no cross-reactions with proinsulin, c-peptide, and glucagon (IMx insulin assay, Abbott Laboratories, Rome, Italy). CV was 7.2 ± 1.7% and 5.7 ± 0.7%, respectively, in the fasting and clamp conditions. Blood samples for FFA assessment were collected in prechilled tubes containing 0.1% EDTA. Tubes were immediately placed in ice and plasma was immediately processed by centrifugation at 4 C. Plasma was then frozen and stored at −70 C, and FFA determinations were performed as previously described (17) within 0–5 working days. CV was 5.9 ± 1.8% and 9.3 ± 3.8%, respectively, in the fasting and clamp conditions.

Calculations

Clamp-based index of insulin sensitivity. The steady-state period of the insulin clamp was defined as the final 30-min period (*i.e.* 120–150 min) during which the CV for blood glucose, plasma insulin, and glucose infusion rate (GIR) was less than 7% and the correlation of each variable with time was not significant. M value was defined as the GIR corrected for the glucose added or removed from the glucose space (space correction) as previously described (10). The glucose clamp-derived index of insulin sensitivity ($S_{I(clamp)}$) was calculated as follows:

TABLE 1. Anthropometric, laboratory, and insulin sensitivity characteristics of the 57 (38F/19M) study subjects

	Average	SD	SEM	Maximum	Minimum
Age (yr)	26.1	4.2	0.6	42	19
Body weight (kg)	62.1	11.5	1.5	87	41
Height (m)	1.70	0.08	0.01	1.86	1.50
Body mass index (kg/m^2)	21.4	2.8	0.4	26.9	16.6
Body fat (kg)	14.9	6.2	0.8	34.1	3.8
Relative body fat (%)	24.7	8.2	1.1	41.4	7.4
Lean body mass (kg)	44.6	8.9	1.1	60.6	29.5
Fasting glucose (mmol/liter)	5.03	0.31	0.04	6.00	4.39
Clamp glucose (mmol/liter)	4.87	0.23	0.03	5.33	4.39
Fasting insulin (pmol/liter)	36.6	17.4	2.4	119.4	15.6
Clamp insulin (pmol/liter)	348.6	51.0	6.6	486.0	221.4
Fasting FFA (mmol/liter)	0.565	0.212	0.028	0.94	0.155
Clamp FFA (mmol/liter)	0.055	0.044	0.006	0.290	0.010
GIR [mg/(kg·min)]	5.43	1.47	0.19	8.49	2.66
$S_{I(clamp)}$ [10^{-4} dl/(min·kg)/(μU/ml)]	12.05	3.21	0.42	20.83	5.30
QUICKI	0.372	0.024	0.003	0.416	0.300
Revised QUICKI	0.418	0.047	0.006	0.573	0.327

$$S_{I(clamp)} = \frac{GIR_{ss}}{G_{ss} \cdot \Delta I_{ss}} \quad (1)$$

where GIR_{ss} is the steady-state glucose infusion rate (mg/kg per min), G_{ss} is the steady-state blood glucose concentration (mg/dl) and ΔI_{ss} is the difference between steady-state and basal insulin concentration (μU/ml) (19).

QUICKI. QUICKI hinges, like HOMA-IR, on the measurement of fasting insulin and glucose concentrations. Whereas HOMA-IR is proportional to the product of fasting insulin and glucose concentrations (13, 14), QUICKI takes both the logarithm and the reciprocal of the glucose-insulin product (15):

$$QUICKI(G_b, I_b) = \frac{1}{\log(G_b \cdot I_b)} = \frac{1}{\log(G_b) + \log(I_b)} \quad (2)$$

where G_b (mg/dl) is the fasting glucose concentration and I_b (μU/ml) is the fasting insulin concentration. Incorporation of the fasting FFA concentration (FFA_b, measured in mmol/liter) into QUICKI leads to a revised QUICKI, which is calculated a follows:

$$\text{revised } QUICKI(G_b, I_b, FFA_b) = \frac{1}{\log(G_b) + \log(I_b) + \log(FFA_b)} \quad (3)$$

Statistical analysis

All data are presented as a mean ± SEM. The relationships $S_{I(clamp)}$ *vs.* QUICKI and $S_{I(clamp)}$ *vs.* revised QUICKI were investigated by means of simple regression analysis. Comparisons between the normal and the offspring group of subjects were performed using the two-tailed unpaired *t* test.

To ascertain how important the relative contribution of fasting glucose, insulin, and FFA concentration to predict insulin sensitivity was, we used the following approach: First, we expressed in a more general way how QUICKI describes the nonlinear relationship between insulin sensitivity and predictor variables; then, by inverting such a relationship, we obtained an expression for insulin resistance as a linear combination of the predictor variables, which allowed us to resort to standard regression techniques to determine their relative importance. The expression that generalizes the way QUICKI describes the relationship between insulin sensitivity (IS) and predictor variables is given by:

$$IS(x_1, x_2, \ldots x_n) = \frac{1}{c_0 + \sum_{i=1}^{n} c_i \log(x_i)} = \frac{1}{c_0 + \sum_{i=1}^{n} c_i y_i} \quad (4)$$

where n is the number of the biochemical variables that contribute to the assessment of insulin sensitivity, x_i is the generic biochemical variable measured in the fasting state, $y_i = \log(x_i)$ is its logarithmic transformation, and c_i ($i = 0,1,\ldots,n$) are constant coefficients that "weight" each variable with respect to the others. Of note is that QUICKI and revised QUICKI are both particular cases of Eq. 4 with weights $c_0 = 0$ and $c_i = 1$ for $i \geq 1$. If one refers to the inverse of IS [*i.e.* insulin resistance (IR)], it becomes simpler to ascertain which variables are more informative. In fact, by taking the inverse of the two members of Eq. 4 one has:

$$IR(x_1, x_2, \ldots x_n) = c_0 + \sum_{i-1}^{n} c_i y_i \quad (5)$$

Eq. 5 states that the relationship between IR and the predictor variables is linear and thus is well suited for being analyzed by standard regression analysis techniques. We used simple regression analysis to determine the association between IR (calculated as the inverse of $S_{I(clamp)}$) and $\log(I_b)$, $\log(G_b)$, and $\log(FFA_b)$, separately. Then we used forward and backward stepwise regression (using F ratio-to-remove of 4 and F ratio-to-enter of 3.996) to assess which of these variables were more relevant as predictors.

Results

Anthropometric and laboratory characteristics of the study subjects

The anthropometric data of the study subjects are summarized in Table 1 together with the plasma glucose, insulin, and FFA concentrations measured in the fasting and insulin-stimulated conditions.

Indices of insulin sensitivity

Clamp-based indices of insulin sensitivity. Clamp-based index of IS are reported in Table 1. As expected, $S_{I(clamp)}$, M value, and GIR were very well correlated with one another ($r = 0.83$, $P < 0.0001$). In addition, both $S_{I(clamp)}$ ($r = -0.40$, $P < 0.01$) and GIR ($r = -0.58$, $P < 0.0001$) were inversely associated with fasting FFA.

Relationship between the clamp-derived indices of insulin sensitivity and HOMA. HOMA-IR was weakly associated with $S_{I(clamp)}$ ($r = 0.23$, $P = 0.09$). The relationship was significantly improved when fasting FFA was incorporated ($r = 0.47$, $P = 0.0002$).

Relationship between the clamp-derived indices of insulin sensitivity and QUICKI. QUICKI was associated with $S_{I(clamp)}$ (Fig. 1, *left panel:* $r = 0.27$, $P < 0.05$) but poorly with GIR ($r = 0.23$, $P = 0.08$). The use of the revised QUICKI markedly improved the relationships with both $S_{I(clamp)}$ (Fig. 1, *right panel:* $r = 0.51$, $P < 0.0001$) and GIR ($r = 0.62$, $P < 0.0001$). The revised QUICKI was associated with $S_{I(clamp)}$ also when data were separately plotted in men ($r = 0.65$, $P < 0.01$), women ($r = 0.41$, $P = 0.01$), offspring of type 2 diabetic parents ($r = 0.56$, $P < 0.02$), and individuals without family history of diabetes ($r = 0.45$, $P < 0.004$).

Comparison between offspring of type 2 diabetic parents and controls

To compare the ability of the revised QUICKI with respect to the QUICKI to detect differences in insulin sensitivity between normal subjects and the offspring of type 2 diabetic parents, a randomized selection of 17 control subjects was performed to obtain tight matching of anthropometric characteristics (Table 2). Fasting plasma glucose and FFA concentrations were significantly increased in the offspring of type 2 diabetic parents with respect to the normal subjects, whereas insulin concentrations were comparable both in the fasting and clamp condition. Impaired insulin sensitivity in the offspring of type 2 diabetic parents was reflected by 21% and 20% reduction in GIR and $S_{I(clamp)}$, respectively, with respect to normal subjects. Whereas HOMA-IR and QUICKI did not detect any significant difference in insulin sensitivity between the two groups, the revised QUICKI found a significant reduction in insulin sensitivity in the offspring group (10%).

Dose-response study of the antilipolytic insulin action

During the low-dose euglycemic hyperinsulinemic clamp, circulating insulin levels increased from 43 ± 4 to 163 ± 14 pmol/liter; meanwhile, during the high-dose clamp, plasma insulin increased similarly to the previous protocol. GIRs

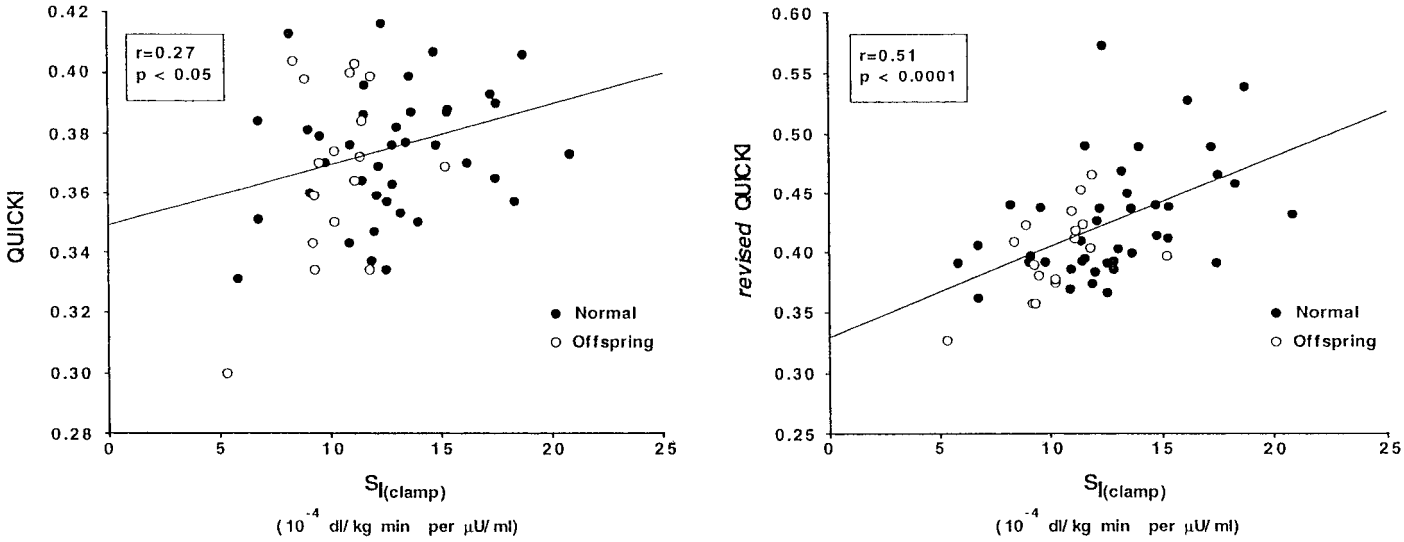

FIG. 1. Correlation between $S_{I(clamp)}$ and QUICKI *(left panel)* and between $S_{I(clamp)}$ and revised QUICKI *(right panel).* Offspring of type 2 diabetic parents are represented by the *empty circles,* normal subjects are represented by the *full circles.*

TABLE 2. Comparison between the offspring of type 2 diabetic parents and controls

	Offspring	Normals	*P*
n (M/F)	17 (9F/8M)	17 (9F/8M)	
Age (yr)	26.5 ± 1.1	25.4 ± 1.1	0.48
Body mass index (kg/m^2)	21.6 ± 0.6	21.8 ± 0.8	0.89
Relative body fat (%)	22.8 ± 1.8	24.6 ± 1.8	0.49
Fasting glucose (mmol/liter)	5.15 ± 0.08	4.93 ± 0.06	0.05
Fasting insulin (pmol/liter)	40.2 ± 6.0	32.4 ± 3.0	0.26
Δ insulin (pmol/liter)	321.0 ± 10.2	333.0 ± 13.8	0.48
Plasma free fatty acids (mmol/liter)	0.634 ± 0.065	0.481 ± 0.051	0.03
GIR [mg/(kg·min)]	4.85 ± 0.25	6.11 ± 0.32	0.004
$S_{I(clamp)}$ [10^{-4} dl/(min·kg)/(μU/ml)]	10.31 ± 0.50	12.89 ± 0.58	0.001
QUICKI	0.368 ± 0.007	0.378 ± 0.005	0.28
Revised QUICKI	0.400 ± 0.009	0.439 ± 0.010	0.006

were 2.62 ± 0.20 and 6.13 ± 0.53 mg/(kg·min), respectively, during the low- and high-dose clamps. Fasting FFA levels (0.577 ± 0.077 mmol/liter) decreased by 64 ± 5% (0.205 ± 0.035 mmol/liter) during the low-dose and by 84 ± 5% (0.094 ± 0.014 mmol/liter) during the high-dose study. FFA levels during the low-dose insulin clamp (which is more appropriate to study the antilipolytic insulin action) were inversely associated with the $S_{I(clamp)}$ calculated during both the low- (r = - 0.57, $P = 0.033$) and high-dose insulin clamp (r = - 0.58, $P = 0.028$).

Linear regression analysis

Table 3 shows the results of the simple and multiple stepwise regression analysis between IR ($IR = 1/S_{I(clamp)}$) and the metabolic predictor variables (*e.g.* log[I_b], log[FFA_b], and log[G_b]). Simple regression analysis showed that, when taken separately, log(I_b) and log(FFA_b) were significantly associated with IR, whereas log(G_b) was not. The multiple stepwise regression analysis selected log(I_b) and log(FFA_b) as the best set of predictors of IR.

Discussion

The results of the present study show that incorporation of fasting plasma FFA concentration into QUICKI improves its association with insulin sensitivity in healthy, nonobese individuals. There are three observations supporting the beneficial effect of calculating a revised QUICKI that includes the contribution of the fasting FFA concentration. First, the revised QUICKI considerably improved the relationship with $S_{I(clamp)}$ with respect to QUICKI (Fig. 1). Second, the revised QUICKI was able to detect a reduction in insulin sensitivity ($P < 0.01$)—that QUICKI was unable to detect ($P = 0.27$)—in a subgroup of individuals with a parent affected by type 2 diabetes in comparison with a subgroup of matched individuals without family history of diabetes (Table 2). Third, the results of the multiple regression analysis indicate that the fasting FFA concentration gives a significant contribution to improve the ability of QUICKI to predict insulin sensitivity (Table 3).

QUICKI is an attractive approach to measure insulin sensitivity in population studies because it is based on a single blood sample and is well correlated with the clamp-based estimate of insulin sensitivity (15). However, QUICKI seems to be less efficient when used to measure insulin sensitivity in the normal range (15). Additional supporting evidence comes from the present study in which we found that QUICKI was unable to detect differences in insulin sensitivity between groups of nonobese individuals with or with-

TABLE 3. Results of the linear regression analysis between insulin resistance and the metabolic predictor variables

	Variable	r	*P* value
Simple regression analysis	$\log(I_b)$	0.39	0.003
	$\log(FFA_b)$	0.31	0.018
	$\log(G_b)$	0.14	0.30
Stepwise multiple regression analysis			
Step 1	$\log(I_b)$	0.39	0.003
Step 2	$\log(I_b)$ and $\log(FFA_b)$	0.52	0.0002

out family history for type 2 diabetes, the former group having a significant 20% reduction in insulin sensitivity, according to the euglycemic hyperinsulinemic clamp. The finding that QUICKI is less powerful when applied to nonobese subjects is probably related to the fact that in this group of individuals, fasting glucose and insulin are both within narrow ranges, which makes it difficult for QUICKI to span with accuracy the wide spectrum of insulin sensitivity characterizing normal individuals. These difficulties motivated our search for an additional postabsorptive metabolic marker of insulin action that could improve the ability of QUICKI to measure insulin sensitivity. We hypothesized that the fasting FFA level might be useful to this purpose because 1) in healthy normal subjects considered to be at high risk of developing diabetes—offspring of type 2 diabetic parents—the postabsorptive plasma FFA concentration was increased in the presence of normal plasma glucose and insulin levels (8, 17, 20, 21); 2) lipolysis is very sensitive to insulin, being that a half-maximal effective dose of insulin for suppression of lipolysis is about 50% of that for suppression of endogenous glucose production (22, 23); and 3) the dose-response study performed in an additional subgroup of 14 individuals showed that FFA levels during the low-dose insulin clamp were inversely associated with $S_{I(clamp)}$ both during the low- and high-dose insulin clamp.

The use of fasting FFA level was beneficial to QUICKI because it strengthened its association with insulin sensitivity (Fig. 1) and also increased its discriminatory power, enabling it to detect a difference in insulin sensitivity between the individuals with or without family history of diabetes (Table 2). The latter finding is of particular importance if QUICKI is to be used in population studies aiming to identify groups at risk of developing diabetes in which the impairment of insulin sensitivity is at an early stage.

The importance of the contribution of FFA concentration to QUICKI was further corroborated by the results of the regression analysis. In our group of nonobese subjects, we found that insulin concentration is the most important correlate of insulin resistance; FFA concentration yields additional, independent information that significantly improves the association with insulin resistance; and glucose concentration has only a minor, nonsignificant role. We speculate that the relative unimportance of glucose as predictor of IR is due to the fact that in normal subjects the glucose-insulin homeostatic system is successful in maintaining glycemia within a very narrow range. It is plausible that the role of glucose as predictor of IR may be more important in obese individuals and in type 2 diabetic patients (*i.e.* in groups in which the homeostatic loop is disturbed).

This study in normal subjects represents a prerequisite, and further work is needed to ascertain whether including the fasting FFA concentration into QUICKI can be useful throughout the entire spectrum of glucose tolerance. What needs to be assessed is whether FFA concentration is still a source of meaningful, independent information on insulin sensitivity also in groups with a higher degree of insulin resistance. Anyway, it is encouraging to find evidence in the literature suggesting that fasting FFA concentration might be helpful in the prediction of insulin resistance also in obese and type 2 diabetic patients. In fact, it has been observed that obese patients with type 2 diabetes mellitus have impaired regulation of lypolisis (23, 24), and that *in vivo* experimental increments of plasma FFA concentrations in healthy humans can induce an IR similar to that observed in type 2 diabetes (25, 26).

In conclusion, this work represents the first attempt to include other metabolic markers, in addition to fasting glucose and insulin, to obtain a more accurate prediction of insulin sensitivity based on a fasting blood sample. Incorporation of the fasting FFA concentration into QUICKI not only improved its association with insulin sensitivity but also enhanced its discriminatory power. Thus, incorporation of the fasting FFA concentration into QUICKI may be helpful for earlier identification of metabolic abnormalities in at-risk subjects and, if validated also in disease states, may contribute to a more widespread use of QUICKI in large-scale or epidemiological studies.

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References

1. **De Fronzo RA** 1988 The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 37:667–687
2. **Lillioja S, Mott DM, Spraul M, et al.** 1993 Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospectives studies of Pima Indians. N Engl J Med 329:1988–1992
3. **Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR** 1990 Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Int Med 113:909–915
4. **Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldener JS, Kahn CR** 1992 Role of glucose and insulin resistance in development of type II diabetes mellitus: results of a 25-year follow-up study. Lancet 340:925–929
5. **Stern MP** 1996 Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? Ann Int Med 124:110–116
6. **Howard G, O'Leary DH, Zaccaro D, et al.** 1996 Insulin sensitivity and atherosclerosis: the Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation 93:1809–1817
7. **Bonora E, Tessari R, Micciolo R, et al.** 1997 Intimal-medial thickness of the carotid artery in nondiabetic and non-insulin-dependent diabetic subjects: relationship with insulin resistance. Diabetes Care 20:627–631
8. **Reaven GM** 1988 Role of insulin resistance in human disease. Diabetes 37: 1595–1607

9. **De Fronzo RA, Ferrannini E** 1991 Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care 14:173–194
10. **De Fronzo RA, Tobin JD, Andres R** 1979 Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 6:E214–E223
11. **American Diabetes Association** 1998 Consensus Development Conference on Insulin Resistance. Diabetes Care 21:310–314
12. **Bergman RN** 1989 Toward physiological understanding of glucose tolerance. Minimal model approach. Diabetes 38:1512–1527
13. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
14. **Bonora E, Targher G, Alberiche M, et al.** 2000 Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 23:57–63
15. **Katz A, Nambi SS, Mather K, et al.** 2000 Quantitative Insulin Sensitivity Check Index: a simple, accurate methods for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 85:2402–2410
16. **Baecke JAH, Burema J, Frijters JER** 1982 A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 36:936–942
17. **Perseghin G, Scifo P, De Cobelli F, et al.** 1999 Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a ^{1}H-^{13}C NMR spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes 48:1600–1606
18. **Monti LD, Sandoli EP, Phan VC, et al.** 1995 A sensitive and reliable method for assaying true human insulin without interaction with human proinsulin-like molecules. Acta Diabetol 32:57–63
19. **Bergman RN, Finegood DT, Ader M** 1985 Assessment of insulin sensitivity *in vivo.* Endocr Rev 6:45–86
20. **Gulli G, Ferrannini E, Stern M, Haffner S, De Fronzo RA** 1992 The metabolic profile of NIDDM is fully establish in glucose tolerant offspring of two Mexican-American NIDDM parents. Diabetes 41:1575–1586
21. **Perseghin G, Ghosh S, Gerow K, Shulman GI** 1997 Metabolic defects in lean nondiabetic offspring of NIDDM parents. A cross-sectional study. Diabetes 46:1001–1009
22. **Nurjhan N, Campbell PJ, Kennedy FP, Miles JM, Gerich JE** 1986 Insulin dose-response characteristics for suppression of glycerol release and conversion to glucose in humans. Diabetes 35:1326–1331
23. **Groop LC, Bonadonna RC, Del Prato S, et al.** 1989 Glucose and free fatty acids metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. J Clin Invest 84:205–213
24. **Swislocki ALM, ChenY-DI, Golay A, Chang M-O, Reaven GM** 1987 Insulin suppression of plasma-free fatty acid concentration in normal individuals and patients with type 2 (non-insulin-dependent) diabetes. Diabetologia 30: 622–626
25. **Boden G, Chen X, Ruiz J, White JV, Rossetti L** 1994 Mechanisms of fatty acid-induced inhibition of glucose uptake. J Clin Invest 93:2438–2446
26. **Roden M, Price TB, Perseghin G, et al.** 1996 Mechanism of free-fatty acid-induced insulin resistance in humans. J Clin Invest 97:2859–2865