

# Fasting Blood Sample-Based Assessment of Insulin Sensitivity in Kidney-Pancreas-Transplanted Patients

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**OBJECTIVE** — To ascertain whether simple indexes of insulin sensitivity based on a fasting blood sample may be reliable measures of insulin sensitivity in combined kidney-pancreas-transplanted patients.

**RESEARCH DESIGN AND METHODS** — Estimates of insulin sensitivity based on fasting plasma glucose, insulin (homeostasis model assessment of insulin sensitivity [HOMA-IS], Quantitative Insulin Sensitivity Check Index [QUICKI]), and free fatty acid (revised QUICKI) concentrations were compared with insulin sensitivity as assessed with the gold standard technique (euglycemic-hyperinsulinemic clamp) in 22 patients who had undergone kidney-pancreas transplantation (KP-Tx) and 18 matched healthy subjects (NOR).

**RESULTS** — In KP-Tx patients, indexes based on the glucose-insulin product, HOMA-IS ( $r = 0.47$ ,  $P = 0.03$ ) and QUICKI ( $r = 0.47$ ,  $P = 0.03$ ), were shown to be reliable measures of insulin sensitivity. The introduction of fasting plasma free fatty acid concentration in the revised QUICKI ( $r = 0.76$ ,  $P < 0.0001$ ) considerably improved the power of prediction of the clamp-based measure of insulin sensitivity as observed in the healthy control subjects ( $r = 0.83$ ,  $P < 0.0001$ ).

**CONCLUSIONS** — This study shows that in KP-Tx patients, HOMA-IS and QUICKI are reliable measures of insulin sensitivity; the additional incorporation of fasting plasma free fatty acid concentration into the glucose-insulin product (revised QUICKI) resulted in a considerably more powerful index.

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The most effective established treatment for patients with type 1 diabetes and kidney failure is achieved with combined kidney-pancreas transplantation (KP-Tx). As of July 2000, >14,000 pancreas transplantations had been reported to the International Pancreas Transplant Registry (IPTR). During the last years, improvements in the surgi-

cal techniques and in the immunosuppressive drug regimens determined a significant increase in patients and graft survival after transplantation as well as freedom from exogenous insulin administration in >80% of cases at 1 year post-transplantation in most centers (1).

Hyperinsulinemia and peripheral insulin resistance caused by systemic

insulin delivery, prednisone therapy (2–4), and organ denervation (5) were recognized consequences of pancreas transplantation. Insulin resistance, presumably induced by steroid therapy, was also found to be a possible cause of acute deterioration of pancreatic graft function (6). The recognition of insulin resistance, therefore, has investigational and clinical relevance in KP-Tx patients.

The insulin clamp technique (7) is considered the “gold standard” (8) for in vivo quantification of insulin sensitivity; however, the method is complex and expensive. A well-accepted alternative is the minimal model analysis of a frequently sampled intravenous glucose tolerance test (9), which is less laborious but is not as simple as required in large-scale studies. Homeostasis model assessment of insulin sensitivity (HOMA-IS) was proposed as a simple and inexpensive tool and is based on the product of the fasting plasma insulin and blood glucose concentrations, measured in a single blood sample, divided by a constant (10). HOMA-IS was shown to be a reliable surrogate measure of in vivo insulin sensitivity in humans when compared with the euglycemic-hyperinsulinemic clamp technique in individuals with various degrees of glucose tolerance and insulin sensitivity (11). Lately, it was proposed that because the distribution of fasting insulin values is skewed, transforming data taking both the logarithm and the reciprocal of the insulin-glucose product might be advantageous; in fact, a better prediction of insulin sensitivity was obtained (12) and the new index has been called the Quantitative Insulin Sensitivity Check Index (QUICKI). Recently, our group showed that the introduction of the logarithm and the reciprocal of plasma free fatty acid (FFA) concentration to the insulin-glucose product was advantageous in nondiabetic individuals with moderate alterations of insulin sensitivity (13). The above-described indexes have been shown to predict insulin sensitivity in conditions classically characterized by in-

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**Abbreviations:** CV, coefficient of variation; FFA, free fatty acid; GIR, glucose infusion rate; KP-Tx, kidney-pancreas transplantation; HOMA-IS, homeostasis model assessment of insulin sensitivity; HOMA-IR, homeostasis model assessment of insulin resistance; NOR, matched healthy subjects; QUICKI, Quantitative Insulin Sensitivity Check Index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—Anthropometric, laboratory, and insulin sensitivity characteristics of the study groups**

	KP-Tx patients (n = 22)	Normal subjects (n = 18)	P
n (men/women)	15/7	11/7	—
On insulin treatment [n (%)]	5 (23%)	—	—
Age (years)	39 ± 9	34 ± 8	0.10
Transplant age (months)	56 ± 21	—	—
BMI (kg/m <sup>2</sup> )	22.3 ± 2.7	24.1 ± 4.0	0.11
Fasting glucose (mmol/l)	5.36 ± 1.30	4.96 ± 0.50	0.20
Clamp glucose (mmol/l)	4.98 ± 0.32	4.89 ± 0.21	0.28
Fasting insulin (pmol/l)	92 ± 50	43 ± 25	<0.01
Clamp insulin (pmol/l)	509 ± 108	417 ± 118	0.02
Δ Insulin (pmol/l)	417 ± 96	374 ± 107	0.18
Fasting FFA (mmol/l)	0.593 ± 0.235	0.536 ± 0.202	0.41
GIR (mg/[kg · min])	4.51 ± 1.71	5.76 ± 1.58	0.02
SI <sub>clamp</sub> (dl/[min · kg]/(μU/ml) × 10 <sup>4</sup> )	7.89 ± 4.13	11.21 ± 3.89	0.01
HOMA-IS	0.370 ± 0.175	0.795 ± 0.323	<0.001
QUICKI	0.325 ± 0.025	0.365 ± 0.027	<0.001
Revised QUICKI	0.359 ± 0.047	0.416 ± 0.055	<0.001

Data are means ± SD.

sulin resistance (type 2 diabetes, obesity) (14), and this study was undertaken to test whether these indexes may be used as predictors of whole-body insulin sensitivity in KP-Tx patients.

## RESEARCH DESIGN AND METHODS

### Subjects

A total of 22 recipients of KP-Tx were studied in the Istituto Scientifico H San Raffaele. Patients received a segmental (n = 7) or whole-organ (n = 15) transplantation with anastomosis of the duodenal segment to the bladder for drainage of exocrine secretions and with systemic venous anastomosis to the iliac vein. Five of these patients needed replacement of insulin via subcutaneous administration to achieve optimal control of glucose homeostasis at the time the study was performed. All patients were in stable clinical and nutritional conditions. A total of 18 healthy subjects matched for anthropometric features served as the control group. Clinical and laboratory characteristics of the study groups are summarized in Table 1. Subjects were fully informed of the possible risk of the study and gave their consent. 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 weeks before the study. Transplanted patients were treated with prednisone, cyclosporine, and azathioprine. Subjects took medications according to the schedule except for prednisone, which was held until completion of the study. Use of other drugs with potential effects on glucose and insulin metabolism was discontinued for a washout period of 1 day. Patients receiving subcutaneous insulin were instructed to take the last doses of intermediate and short-acting insulin 24 and 12 h, respectively, before the euglycemic-hyperinsulinemic clamp, which was performed to assess insulin sensitivity after a 10-h overnight fast.

### 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 7:00 A.M. after a 10-h overnight fast. A Teflon catheter was inserted into an ante-cubital vein for infusion and an additional catheter 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 FFA were performed in triplicate. Thereafter, a euglycemic-hyperinsuline-

mic clamp was performed as previously described (13,15). Insulin was infused at 40 mU/[m<sup>2</sup> · min] to reach a plasma insulin concentration of ~450 pmol/l, and plasma glucose concentration was kept at 5 mmol/l for 150 min by means of a variable infusion of 20% dextrose. Blood samples for plasma insulin, glucose, and FFA were collected every 15 min throughout the study.

### Analytical procedures

Plasma glucose was measured with a Beckman glucose analyzer (Beckman, Fullerton, CA) (13,15) and coefficient of variation (CV) was 1.5 ± 0.1 and 2.5 ± 0.2% in the fasting and clamp conditions, respectively. Plasma-free insulin was measured by means of radioimmunoassay (Incstar, Stillwater, MN) as previously described (3). CV was 8.2 ± 0.9 and 3.1 ± 0.7% in the fasting and clamp conditions, respectively. Blood samples for assessment of FFA were collected in prechilled tubes containing 0.1% EDTA. Tubes were immediately placed on ice and plasma was immediately processed by centrifugation at 4°C. Plasma was then frozen and stored at -70°C, and determination of FFA was performed as previously described (13,15) within 0–5 working days. CV was 7.1 ± 1.5 and 12.1 ± 1.5% in the fasting and clamp conditions, respectively.

### Calculations

The glucose infusion rate (GIR) was measured in steady-state conditions during the 120–150 min of the insulin clamp and expressed as mg/[kg · min]; CV was 2.0 ± 0.2%. Insulin sensitivity (SI<sub>clamp</sub>) was calculated as follows: GIR/(ΔI × G), where ΔI is the increment of plasma insulin concentrations during the 120–150 min of the clamp with respect to the basal condition, and G is the plasma glucose concentration during the 120–150 min of the clamp (16). Homeostasis model assessment provided equations for estimating insulin resistance (HOMA-IR)

$$\text{HOMA-IR} = G_0 \cdot I_0 / 22.5 \quad (1)$$

or insulin sensitivity

$$\text{HOMA-IS} = 1/\text{HOMA} \quad (2)$$

where I<sub>0</sub> (μU/ml) is the fasting insulin concentration, G<sub>0</sub> (mmol/l) is the fasting glucose concentration, and 22.5 repre-

sents a constant applied to correct the value to unity as previously described (10). QUICKI was calculated as previously described (12).

$$\text{QUICKI} = 1/[\log(I_0) + \log(G_0)] \quad (3)$$

Incorporation of FFA into QUICKI generated a revised QUICKI, which was calculated as follows (13)

$$\text{revised QUICKI} = 1/[\log(I_0) + \log(G_0) + \log(\text{FFA}_0)] \quad (4)$$

where  $\text{FFA}_0$  (mmol/l) is the fasting FFA concentration.

### Statistical analysis

All data are presented as a mean  $\pm$  SE. The steady state was defined as a nonsignificant correlation with time ( $P > 0.05$ ) of the variable using standard linear regression. Relationship between variables was assessed by means of simple correlation ( $r$ ) analysis. Comparisons between the normal and KP-Tx patients were performed using the two-tailed unpaired Student's  $t$  test.

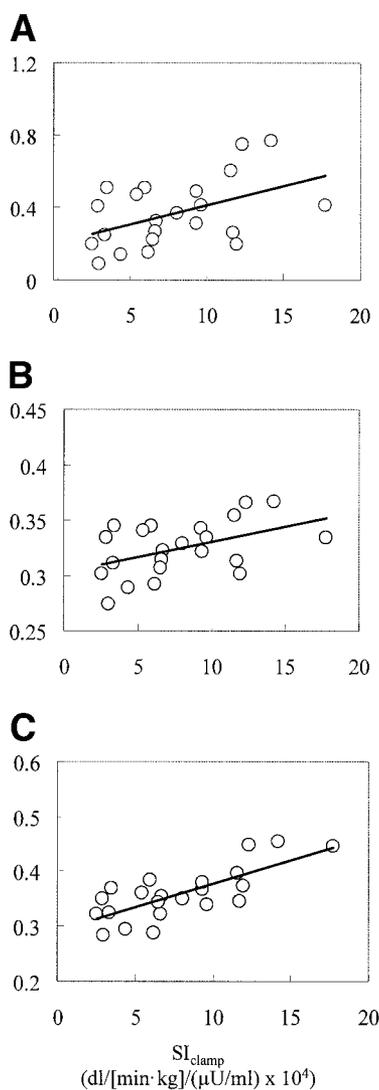
## RESULTS

### Anthropometric and laboratory characteristics of the study subjects

The anthropometric parameters of study subjects are summarized in Table 1. The two study groups were matched for anthropometric features. Age, sex, BMI, and fasting plasma glucose and FFA concentrations were not different between groups. On the contrary, KP-Tx patients were characterized by marked hyperinsulinemia when compared with normal subjects ( $P < 0.01$ ).

### Insulin sensitivity in KP-Tx patients

GIR and  $\text{SI}_{\text{clamp}}$ , HOMA-IS, QUICKI, and revised QUICKI were all significantly reduced in KP-Tx patients when compared with normal subjects (Table 1). Fasting plasma glucose was not associated with GIR ( $r = -0.31$ ,  $P = 0.17$ ) and  $\text{SI}_{\text{clamp}}$  ( $r = -0.34$ ,  $P = 0.13$ ), and the same was observed for fasting plasma insulin ( $r = -0.42$ ,  $P = 0.07$  and  $r = -0.35$ ,  $P = 0.11$ , respectively). On the contrary, fasting plasma FFA concentration was associated with both GIR ( $r = -0.63$ ,  $P < 0.002$ ) and  $\text{SI}_{\text{clamp}}$  ( $r = -0.67$ ,  $P < 0.001$ ). GIR was associated with



**Figure 1**—The relationships between the  $\text{SI}_{\text{clamp}}$  (x-axis) with HOMA-IS (A), QUICKI (B), and revised QUICKI (C) in KP-Tx patients. For HOMA-IS and QUICKI,  $r = 0.47$ ,  $P = 0.03$ ; for revised QUICKI,  $r = 0.76$ ,  $P < 0.0001$ .

HOMA-IS ( $r = 0.43$ ,  $P < 0.05$ ), QUICKI ( $r = 0.46$ ,  $P = 0.03$ ), and revised QUICKI ( $r = 0.67$ ,  $P < 0.0002$ ) as well as the  $\text{SI}_{\text{clamp}}$  ( $r = 0.47$ ,  $P = 0.03$  with respect to HOMA-IS;  $r = 0.47$ ,  $P = 0.03$  with respect to QUICKI; and  $r = 0.76$ ,  $P < 0.0001$  with respect to revised QUICKI) (Fig. 1).

### Insulin sensitivity in the normal healthy subjects

In the normal subjects, GIR and  $\text{SI}_{\text{clamp}}$  fasting plasma glucose were not associated with GIR ( $r = -0.23$ ,  $P = 0.32$ ) or  $\text{SI}_{\text{clamp}}$  ( $r = -0.09$ ,  $P = 0.69$ ). However, fasting plasma insulin ( $r = -0.57$ ,  $P <$

$0.01$  and  $r = -0.71$ ,  $P < 0.001$  with respect to GIR and  $\text{SI}_{\text{clamp}}$ , respectively) and fasting plasma FFA ( $r = -0.76$ ,  $P < 0.001$  and  $r = -0.60$ ,  $P < 0.01$  with respect to GIR and  $\text{SI}_{\text{clamp}}$ , respectively) were significantly associated with both GIR and  $\text{SI}_{\text{clamp}}$ . GIR was significantly associated with HOMA-IS ( $r = 0.55$ ,  $P < 0.02$ ), QUICKI ( $r = 0.58$ ,  $P < 0.002$ ), and revised QUICKI ( $r = 0.87$ ,  $P < 0.0001$ ). When  $\text{SI}_{\text{clamp}}$  was used as clamp-derived estimate of insulin sensitivity, the same trend was observed ( $r = 0.69$ ,  $P < 0.001$  with respect to HOMA-IS;  $r = 0.71$ ,  $P < 0.0001$  with respect to QUICKI; and  $r = 0.83$ ,  $P < 0.0001$  with respect to revised QUICKI).

**CONCLUSIONS**— This study showed that in KP-Tx recipients, HOMA-IS, QUICKI, and revised QUICKI may be used as measures of insulin sensitivity as assessed with the insulin clamp (Fig. 1), but the revised QUICKI, incorporating the fasting plasma FFA levels, considerably improved the association with insulin sensitivity and was more reliable than the other indexes.

HOMA-IS and QUICKI have been proposed to predict insulin sensitivity in classical conditions of insulin resistance. Whether they may be useful surrogates of insulin sensitivity in KP-Tx patients has never been assessed before. The surgical procedure of KP-Tx usually foresees the anastomosis of the pancreas to the iliac vein; the liver, which normally clears on the first pass 40–60% of the insulin secreted by the pancreas, is therefore bypassed in this procedure, determining in these patients an overall reduction of insulin clearance (17). In agreement with this fact, KP-Tx patients studied in this work showed a significant increment of fasting plasma insulin levels (Table 1), and we also observed that the relationship between clamp-based insulin sensitivity and fasting plasma insulin, detectable in the healthy matched control subjects ( $r = -0.71$ ,  $P = 0.005$ ), was lost in the KP-Tx patients ( $r = -0.35$ ,  $P = 0.11$ ). A different situation was observed with respect to the other variables included in HOMA-IS and QUICKI; in fact, the relationship with fasting plasma glucose in KP-Tx patients was not significant ( $r = -0.33$ ,  $P = 0.11$ ), but it was not worse than the relationship observed in the group of control subjects ( $r = 0.09$ ,  $P = 0.70$ ), in which fasting plasma glucose was also less infor-

mative than fasting plasma insulin levels. These findings may partially explain the reduced association of  $SI_{\text{clamp}}$  with HOMA-IS and QUICKI detected in KP-Tx patients with respect to the healthy, normal subjects (Fig. 1) and may suggest that the reason for this reduced association mainly resides in a reduced association with fasting plasma insulin.

These findings, the well-known association of increased plasma FFA concentration with insulin resistance in diabetes (13,18,19) and hypertension (20,21), our previous observations of the inverse association of fasting plasma FFA concentration with insulin sensitivity as assessed with the insulin clamp (19), and the fact that revised QUICKI, incorporating the logarithm and the reciprocal of FFA concentration to the insulin-glucose product, was better than QUICKI in normal individuals and in subjects with moderate alterations of insulin sensitivity (13), suggest that in KP-Tx patients, additional metabolic markers of insulin action could be profitably taken into account to improve its association with insulin sensitivity. Whether the antilipolytic action of insulin is impaired or unaffected in KP-Tx patients is controversial (22,23); nevertheless, the fasting FFA levels were homogeneously found to be not different than in control subjects (23,24). In this study, fasting plasma FFA concentration in KP-Tx patients was also found to be comparable to that of control subjects, and its association with the clamp-based index of insulin sensitivity was significant in the group of healthy subjects ( $r = -0.60$ ,  $P < 0.005$ ) and in the KP-Tx patients ( $r = -0.67$ ,  $P < 0.001$ ). As a consequence, the incorporation of fasting plasma FFA concentration into QUICKI considerably improved the relationship of the revised QUICKI with  $SI_{\text{clamp}}$ , especially in KP-Tx patients (Fig. 1).

Graft failure determines recurrence of diabetes in a significant subset of pancreatic graft recipients (1), but identification of subjects at risk is difficult and often delayed. Appropriate prevention and treatment are not feasible because of the lack of diagnostic accuracy of available biochemical parameters and imaging tools. Our group showed that the only variable that is able to predict the return to diabetic state for any cause in KP-Tx was the mean daily glucose concentration (25), but the small sample size in which insulin sensitivity was assessed using the

insulin clamp limited the power of the statistical inference regarding insulin resistance. In a larger scale study, the use of these indexes based on fasting data might clarify the impact of metabolic abnormalities on graft failure.

In conclusion, in KP-Tx patients, HOMA-IS and QUICKI are reliable measures of insulin sensitivity. The association with insulin sensitivity is considerably improved if FFA concentration is taken into account (revised QUICKI). Revised QUICKI may be tested for earlier identification of metabolic abnormalities in subjects at risk for deterioration of pancreatic graft function and development of cardiovascular disease and may contribute to large-scale or epidemiological studies in these patients. This study represents a necessary prerequisite, and further work is needed to ascertain whether including the fasting FFA concentration in QUICKI can be applicable to other models of  $\beta$ -cell function replacement, such as isolated pancreas transplantation, pancreas transplantation with portal anastomosis, and islet transplantation.

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