

Family History of Diabetes as a New Determinant of Insulin Sensitivity and Secretion in Patients Who Have Undergone a Simultaneous Pancreas-Kidney Transplant

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Abstract

Objectives: We used homeostasis model assessment to investigate insulin sensitivity and secretion after a simultaneous pancreas-kidney transplant or kidney transplant alone. In that model, fasting plasma glucose and C-peptide levels are used to evaluate insulin sensitivity and beta-cell function.

Materials and Methods: Factors (eg, age, sex, race, delayed kidney allograft function) were correlated with homeostasis model assessment of beta-cell function and homeostasis model assessment of insulin sensitivity values after simultaneous pancreas-kidney transplant (n=89) or kidney transplant alone (n=68), and the results were compared with those in healthy subjects (n=49).

Results: Homeostasis model assessment of beta-cell function values were similar in patients who underwent kidney transplant alone or a simultaneous pancreas-kidney transplant, and were higher than homeostasis model assessment of beta-cell function values in healthy subjects. The homeostasis model assessment of insulin sensitivity showed intermediate values for patients who underwent a simultaneous pancreas-kidney transplant and correlated with prednisone dosages (in those who underwent kidney transplant alone) and tacrolimus levels (in patients who underwent a simultaneous pancreas-kidney transplant). Homeostasis model assessment of beta-cell function

values correlated with prednisone dosages in both groups and with tacrolimus levels in only those who underwent a simultaneous pancreas-kidney transplant. The body mass index of subjects who underwent kidney transplant alone correlated with both homeostasis model assessment of beta-cell function results and homeostasis model assessment of insulin sensitivity results. A family history of diabetes in subjects who underwent a simultaneous pancreas-kidney transplant correlated with homeostasis model assessment of beta-cell function results and homeostasis model assessment of insulin sensitivity results.

Conclusions: Immunosuppressive regimen and body mass index were linked with reduced insulin sensitivity after kidney transplant. A family history of diabetes was linked with higher values of insulin secretion and lower insulin sensitivity in patients who underwent a simultaneous pancreas-kidney transplant.

Key words: HOMA, Insulin secretion, Insulin sensitivity, Pancreas transplant

Pancreas-kidney transplant is an effective treatment for patients with insulin-dependent diabetes and chronic renal failure (1). Pancreas allograft survival is determined by several factors, such as technical failure during transplant surgery, acute or chronic rejection, recurrence of autoimmunity, and toxicity caused by immunosuppression (2, 3). All of those factors decrease the beta-cell mass and/or increase insulin resistance (4-9). Tacrolimus inhibits insulin secretion in a dose-dependent manner and is associated with beta-cell apoptosis (5), and glucocorticoids increase insulin resistance (7). Other factors (metabolic syndrome, weight gain, a family history of diabetes) may have important roles in the

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glycemic changes that often occur after solid-organ transplant (10).

The progression to diabetes involves several stages, characterized by changes in beta-cell mass, phenotype, and function (11). The glycemic dysfunction that occurs after transplant may be caused by similar factors. Augmented insulin secretion that causes overload of the beta-cell mass is followed by progressive beta-cell dysfunction and death. The euglycemic-hyperinsulinemic clamp is an accurate tool for evaluating insulin resistance, but it is complex to use and invasive (factors that limit its use in many patients). The homeostasis model assessment (HOMA) of insulin resistance, which is a useful surrogate index of insulin resistance in diabetic and nondiabetic subjects (12, 13), is a mathematical assessment of the interaction between beta-cell function and insulin resistance. It is based on the assumption that an increasing glucose level causes a compensatory increase in the level of insulin. That model is useful in clinical and epidemiologic studies (14) and may be used to assess the response to antidiabetic drugs, to estimate the likelihood of cardiovascular disease in people with type 2 diabetes, and to evaluate the risk for diabetes (15, 16).

The HOMA of insulin resistance has been used in stable renal transplant patients (17) and in those who have undergone a simultaneous pancreas-kidney transplant (18). The HOMA of beta-cell function is used to evaluate basal insulin secretion, and the HOMA of insulin resistance is used to assess insulin sensitivity.

The first 2 objectives of this study were to correlate HOMA of beta-cell function results and HOMA of insulin sensitivity values with the use of glucocorticoids and tacrolimus dosages and levels in nonobese, nondiabetic kidney transplant alone recipients, and in simultaneous pancreas-kidney transplant recipients, with normal pancreas allograft function, and to compare the results with those of healthy subjects. The third objective was to find the key factors implicated in a higher HOMA index in patients who underwent a simultaneous pancreas-kidney transplant.

Materials and Methods

Subjects and clinical data

This study was approved by the Ethics Committee of the Federal University of São Paulo, and all

participants provided written, informed consent; all protocols adhered with the ethical guidelines of the 1975 Helsinki Declaration. Over 5.5 years (December 2000-August 2006), 150 simultaneous pancreas-kidney transplants were performed at the Universidade Federal de São Paulo in São Paulo, Brazil. All patients studied had a history of insulin-dependence before transplant and chronic renal failure. In Brazil, pancreas and kidney allocation for a simultaneous pancreas-kidney transplant is not determined by human leukocyte antigen matching (as it is in other parts of the world) but rather, by the length of time (average, 2 years) that a candidate remains on a transplant waiting list. All insulin-dependent patients are eligible for a simultaneous pancreas-kidney transplant, but only patients with type 1 diabetes and adults with latent autoimmune diabetes were selected for this study. In those subjects, the mean durations of diabetes and dialysis were 21.9 ± 5.9 years (range, 10-37 years) and 26 ± 17.5 months (range, 0-108 months). Enteric drainage was performed in 143 patients (7 patients underwent bladder drainage). Either iliac venous or inferior cava vein anastomosis was done in all subjects.

Of 150 patients, 50% were men, 16.2% were black, 4% were Asian, and 79.8% were white. The initial immunosuppressive regimen included tacrolimus 0.15 mg/kg/d, the dosage of which was adjusted during the posttransplant period to maintain serum levels ranging from 10-15 ng/mL in the first 30 days of treatment and 8-10 ng/mL between 31 and 90 days of therapy; this was followed by a maintenance dosage of 5-10 ng/mL. The initial dosage of prednisone was 30 mg/d; that was reduced by 5 mg each month until the eighth month of treatment, when the maintenance dosage of 5 mg/d was reached. Mycophenolate mofetil 2 g/d or mycophenolate sodium 1.44 g/d was administered to all patients studied. Induction with monoclonal or polyclonal antibodies was not routinely performed. However, induction was performed in patients who underwent a retransplant, experienced cold ischemia of the organ that persisted longer than 24 hours, or exhibited a panel-reactive antibody level of higher than 20%.

In our study, data from 89 recipients of a simultaneous pancreas-kidney transplant were available for clinical and laboratory analyses. Patients with pancreas allograft loss owing to technical failure or rejection, cyclosporine or sirolimus recipients, and patients treated with insulin or an antidiabetic drug

were excluded from the study. Only patients with a body mass index of less than 30 kg/m² and a fasting plasma glucose level of less than 100 mg/dL were included. The control group consisted of 68 nondiabetic healthy kidney transplant recipients. Of those subjects, 40 received a kidney from a living donor (77.5% haploidentical donors and 22.5% distinct donors), and 28 received a kidney from a deceased donor. All subjects were treated with the same immunosuppressive regimen (tacrolimus, prednisone, and either mycophenolate or azathioprine) as described above.

It has been the policy of our unit to administer prednisone 10 mg/d to most patients who have undergone kidney transplant alone. In our study, all of those subjects demonstrated stable allograft function, and their treatment was adjusted to maintain a therapeutic serum level of tacrolimus. The body mass index of those patients was less than 30 kg/m², and their fasting plasma glucose level was less than 100 mg/dL. In addition, 49 healthy subjects with a body mass index of less than 30 kg/m² were included as a control group, and their fasting plasma glucose, fasting plasma C-peptide, and creatinine levels were assessed.

Laboratory data

After an overnight fast of at least 8 hours, samples of venous blood were used to measure the concentrations of glucose, C-peptide, and creatinine in the plasma. The plasma glucose level was measured with the glucose-oxidase method. The C-peptide level (reference range, 1.1-5 ng/mL) was measured with a competitive chemiluminescent enzyme immunoassay (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA). The plasma creatinine level was measured with the Jaffe alkaline picrate method (reference range for women, 0.6-1.0 mg/dL; reference range for men, 0.8-1.2 mg/dL). Tacrolimus levels were measured with the IMx tacrolimus microparticle enzyme immunoassay method (Abbott Laboratories, Abbott Park, IL, USA), and samples were collected at least 12 hours before the morning dose. Serum creatinine clearance rates were calculated with a modification of the following formula for evaluating renal disease, which in a study by Poggio and colleagues (19), was used, as explained below, to estimate the glomerular filtration ratio and was validated in renal transplant recipients including subjects treated with calcineurin inhibitors:

Estimation glomerular filtration based on

Modification of Diet in Renal Disease = $186 \times (\text{serum creatinine level [mg/dL]} - 1.154 \times [\text{age (y)}] - 0.203 \times [0.742 \text{ for female sex}] \times [1.212 \text{ for black race}])$

Assessment of insulin sensitivity and secretion

The homeostatic model assessment was performed with the following equations:

Homeostasis model assessment of insulin sensitivity = $1/\text{homeostasis model assessment of insulin resistance}$.

Homeostasis model assessment of insulin resistance = $(\text{fasting plasma C-peptide level [nmol/L]} \times \text{fasting plasma glucose level [mg/dL]}) / 22.5$. Homeostasis model assessment of beta-cell function = $(20 \times \text{fasting plasma C-peptide [nmol/L]} / [\text{fasting plasma glucose (mg/dL)} - 3.5])$, expressed in a percentage.

The fasting plasma C-peptide level (instead of the fasting plasma insulin level) was used in the formulations above because it reflects endogenous insulin secretion, it is not affected by hepatic metabolism, and most of it is eliminated by the kidneys. Moreover, C-peptide analysis is not affected by insulin antibodies. The conversion of C-peptide from nanograms per milliliter to nanomoles per liter is 1 ng/mL = 0.33 nmol/L, and that of fasting plasma glucose from milligrams per deciliter to millimoles per liter is 1 mg/dL = 0.056 mmol/L.

Normal insulin sensitivity was defined by a Brazilian study in which the HOMA of insulin resistance was used in 1898 healthy subjects who ranged in age from 18 to 90 years, and whose fasting glucose level was less than 99 mg/dL. The HOMA of insulin resistance ranged according to body mass index as follows with a mean of 1.8 ± 0.9 kg/m², body mass index < 25 kg/m²; 1.2 ± 0.65 kg/m²; body mass index 25-30 kg/m², 1.8 ± 0.98 kg/m²; and body mass index > 30 kg/m², 2.9 ± 1.6 kg/m². In our study, normal insulin sensitivity was defined in healthy subjects with a body mass index of less than 25 kg/m². Those values were greater than 0.8 (20).

Traditional and transplant-related factors

Parameters included in the analysis of simultaneous pancreas-kidney transplant recipients were age, sex, race, delayed kidney allograft function (days of oliguria or necessity for dialysis), pancreas cold ischemia time (14.3 ± 3.8 hours; range, 5-22 hours), acute kidney allograft rejection (in 23.6% of the patients studied) and cytomegalovirus infection (in 30% of the patients studied). Delayed kidney allograft function was reported in 14.6% of the study subjects. In most

Brazilian transplant centers, the prophylaxis against cytomegalovirus is not routine because it is expensive. The cytomegalovirus serologic status was donor positive/recipient negative in less than 5% of the patients. Additional parameters, such as creatinine clearance, were assessed by the Modification of Diet in Renal Disease formula, and body mass index was calculated by dividing the patient's weight in kilograms by his or her height in square meters.

Our analysis consisted of information obtained from patients treated with statins, angiotensin-II receptor blockers, angiotensin-converting enzyme inhibitors, glucocorticoids, and tacrolimus (in levels and doses per kilogram). A family history of diabetes of first-degree relatives was found in 19.1% of the patients studied. Donor data included age, sex, and cause of death (trauma or nontrauma). Analytic parameters for patients who underwent kidney transplant alone included the recipient's age, sex, race, body mass index, serum level of tacrolimus, and number of dosages of tacrolimus and prednisone.

Statistical analysis

All results were reported as the mean $\pm$ SD unless otherwise indicated. Statistical analyses were performed with SPSS software (Statistical Product and Service Solutions, version 12.0, SSPS Inc, Chicago, IL, USA). The Fisher exact test and an analysis of variance were used for numerical variables, and the Pearson chi-square test was used for categorical variables. The Pearson product moment correlation test was used for correlations. To determine which traditional and transplant-related factors were associated with HOMA indexes, all putative factors that were univariately associated at $P \leq 0.3$ were entered simultaneously in a linear regression model with HOMA of beta-cell function or HOMA of insulin sensitivity as the dependent variable. Values for $P < .05$ were considered statistically significant.

Results

Demographic data are shown in Table 1, and fasting plasma glucose, basal C-peptide, and HOMA indexes among groups are described in Table 2. Homeostasis model assessment of beta-cell function values were similar in the simultaneous pancreas-kidney transplant and the kidney transplant alone groups ($P = .6$) but higher than those in the healthy subjects ($P < .0001$) (Table 2). The HOMA of insulin sensitivity index

Table 1. Demographic data from the study subjects.

Variables	Control group (healthy) (n=49)	Simultaneous pancreas-kidney transplant group (n=89)	Kidney transplant alone group (n=68)	P value
Age (y)	39.1 $\pm$ 1.5	34.7 $\pm$ 0.6	34.3 $\pm$ 1.7*	.02
Male sex (%)	42.8	48.5	47.8	1.0
Black race (%)	18.4	30	30.4	1.0
Body mass index (kg/m ²)	24.6 $\pm$ 0.5	22.1 $\pm$ 0.3	24 $\pm$ 0.5†	.0001
Time after transplant (d)	-	474 $\pm$ 44	543 $\pm$ 66	.37
Mean doses of glucocorticoids (mg/kg)	-	0.18 $\pm$ 0.02	0.2 $\pm$ 0.02	.4
Mean doses of tacrolimus (mg/kg)	-	0.13 $\pm$ 0.01	0.14 $\pm$ 0.01	.6
Serum levels of tacrolimus (ng/mL)	-	8.6 $\pm$ 0.4	8.7 $\pm$ 0.6	.9
Creatinine (mg/dL)	1.0 $\pm$ 0.03	1.26 $\pm$ 0.04	1.36 $\pm$ 0.04‡	< .0001
Creatinine clearance-Modification of Diet in Renal Disease (mL/min/1.73 m ²)	103.5 $\pm$ 4.4	66.7 $\pm$ 2.1	63.2 $\pm$ 2.2§	< .0001
Hypertension (%)	-	44	62.3	.03
ARB/ACEI use (%)	-	69.2	16.3	< .0001
Statin use (%)	-	66.3	7.2	< .0001

* $P = .8$, Simultaneous pancreas-kidney transplant group vs kidney transplant alone group.

† $P = .4$, Control (healthy) group vs kidney transplant alone group.

‡ $P = .1$, Simultaneous pancreas-kidney transplant group vs kidney transplant alone group.

§ $P = .2$, Simultaneous pancreas-kidney transplant group vs kidney transplant alone group.

Abbreviations: ARB, Angiotensin-II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors.

values were lower in the kidney transplant alone group, which suggests that kidney transplant alone is associated with lower levels of insulin sensitivity than those in healthy subjects or the simultaneous pancreas-kidney transplant group ($P < .0001$ and $P = .0001$, respectively). In patients who underwent a simultaneous pancreas-kidney transplant, insulin sensitivity was lower than that in healthy subjects ($P = .01$).

When we correlated body mass index with insulin sensitivity and beta-cell function, we found that in healthy subjects, body mass index had a weak negative correlation with the HOMA of insulin sensitivity ($P = .047$). In patients who underwent kidney transplant alone, HOMA of beta-cell function values had a positive correlation with body mass index ($P = .03$), and HOMA of insulin sensitivity values had a negative correlation ($P = .045$) (Figures 1 and 2). In patients who underwent a simultaneous pancreas-kidney transplant, there was no correlation between the body mass index and either index (HOMA of beta-cell function, $P = .82$; or the HOMA of insulin sensitivity, $P = .06$).

Table 2. Glucose levels, C-peptide levels, HOMA of beta-cell function, and HOMA of insulin sensitivity in the study subjects.

Variables	Control group (healthy) (n=49)	Simultaneous pancreas-kidney transplant group (n=89)	Kidney transplant alone group (n=68)	P value
Fasting plasma glucose level (mg/dL)	89.1 ± 1.4	83.7 ± 1.3	88.8 ± 1.9*	.02
Basal C-peptide level (ng/mL)	2.2 ± 0.2	2.9 ± 0.1	3.7 ± 0.2	< .0001
HOMA of beta-cell function (%)	137.2 ± 8.02	193.2 ± 8.8	200.4 ± 9.02†	< .0001
HOMA of insulin sensitivity	0.8 ± 0.06	0.6 ± 0.03	0.45 ± 0.02	< .0001

*P = .9, Control (healthy) group vs kidney transplant alone group.

†P = .6, Simultaneous pancreas-kidney transplant group vs kidney transplant alone group.

Abbreviation: HOMA, homeostasis model assessment.

Tables 3 and 4 show the univariate and multivariate analyses of traditional and transplant-related risk factors that modified HOMA of beta-cell function and the HOMA of insulin sensitivity after a simultaneous pancreas-kidney transplant. Homeostasis model assessment of beta-cell function values were $224.3\% \pm 123.6\%$ in subjects with a family history of diabetes and $185.7\% \pm 72.9\%$ in those with no family history of diabetes ($P = .036$). Homeostasis model assessment of insulin sensitivity values were

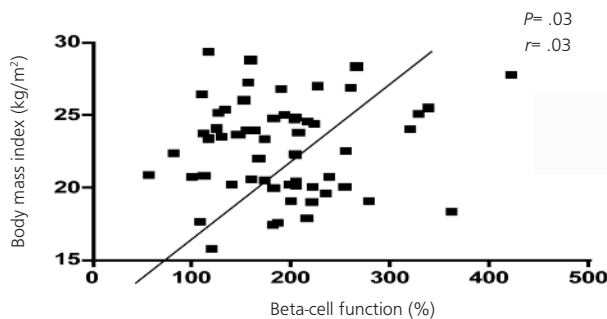


Figure 1. HOMA of beta-cell function.

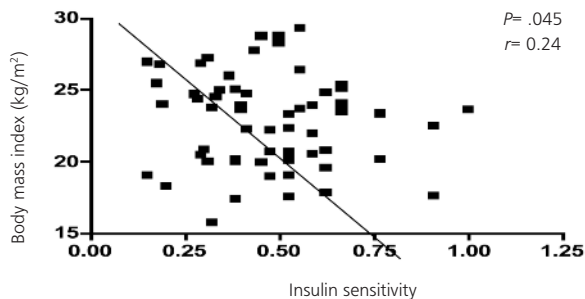


Figure 2. HOMA of insulin sensitivity.

Table 3. Univariate analysis of factors influencing HOMA of beta-cell function and HOMA of insulin sensitivity after a simultaneous pancreas-kidney transplant.

Variables +	Homeostasis model of assessment of beta-cell function	Homeostasis model of assessment of insulin sensitivity
Variable	P Value	P Value
Recipient's age (y)	.22	.17
Recipient's sex	.52	.58
Recipient's race	.83	.62
Duration of diabetes (y)	.64	.78
Duration of treatment with dialysis (mo)	.21	.02
Pancreas cold ischemia (h)	1.0	.19
Tacrolimus dose (mg/kg)	.88	.24
Tacrolimus levels (ng/mL)	.02	.002
Prednisone dose (mg/kg)	.003	.36
Recipient's body mass index (kg/m²)	.88	.06
Statin use	.94	.89
ARB/ACEI use	.69	.32
Cytomegalovirus infection	.31	.9
Delayed kidney allograft function	.51	.38
Acute kidney rejection	.74	.63
Family history of diabetes	.18	.03
Donor age (y)	.44	.21
Donor sex (61.3% male; 38.7% female)	.47	.06
Cause of donor brain death	.47	.55

Abbreviations: BMI, Body mass index; ARB, angiotensin-II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors.

Table 4. Multivariate analysis of factors influencing HOMA of beta-cell function and HOMA of insulin sensitivity after simultaneous pancreas-kidney transplant or kidney transplant alone.

Simultaneous pancreas-kidney transplant group		P Value	Standardized coefficient β	95% CI	
				lower	upper
HOMA of beta-cell function	Prednisone dose (mg/kg)	.029	0.48	1.34	23.98
	Tacrolimus level	.002	0.93	21.64	876.49
	Family history of diabetes	.044	0.22	1.25	89.81
HOMA of insulin sensitivity	Tacrolimus level	.001	−0.38	−0.06	−0.017
	Family history of diabetes	.023	−0.24	−0.36	−0.027
Kidney transplant alone		P	Standardized coefficient β	95% CI	
				lower	upper
HOMA of beta-cell function	Prednisone dose (mg/kg)	.03	0.38	1.97	10.22
	Body mass index	.04	0.49	22.36	428.8
HOMA of insulin sensitivity	Prednisone dose (mg/kg)	.001	−0.41	−0.77	−0.2
	Body mass index	.001	−0.41	−0.027	−0.007

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA, homeostasis model assessment.

influenced by tacrolimus levels ($P = .001$) and by a family history of diabetes ($P = .023$). Homeostasis model assessment of insulin sensitivity mean values for recipients with a family history of diabetes were 0.49 ± 0.18 , and they were 0.62 ± 0.33 for those with no family history of diabetes ($P = .033$).

In patients who underwent kidney transplant alone, both HOMA of beta-cell function and the HOMA of insulin sensitivity were influenced by prednisone ($P = .03$ and $P = .001$, respectively) and body mass index ($P = .04$ and $P = .001$, respectively) (Table 4). The recipient's age, sex, race, and tacrolimus dosages and levels had no significant effect on HOMA indexes after kidney transplant alone.

Discussion

In this study, we analyzed traditional and transplant-related factors that modified HOMA indexes in the simultaneous pancreas-kidney transplant and kidney transplant alone groups. Homeostasis model assessment of beta-cell function values were similar in both transplant groups and were higher than the values in healthy subjects. Homeostasis model assessment insulin sensitivity values were 50% lower in patients who underwent a simultaneous pancreas-kidney transplant than in healthy subjects and patients who underwent kidney transplant alone.

The HOMA of beta-cell function values correlated with prednisone dosages in both groups and with tacrolimus levels in the simultaneous pancreas-kidney transplant group. Body mass index correlated with HOMA of beta-cell function in the kidney transplant alone group but not in the simultaneous pancreas-kidney transplant group. A family history of diabetes was associated with indexes of HOMA of beta-cell function and HOMA of insulin sensitivity in the simultaneous pancreas-kidney transplant group but not in the kidney transplant alone group.

Kidney transplant alone homeostasis model assessment

The applicability of HOMA, which was limited in our kidney transplant alone group, may be used to identify insulin resistance in patients with increased cardiovascular risk or potentially impaired long-term renal allograft function owing to weight gain (21-23). That model also can be used to identify patients at great risk of developing posttransplant diabetes

mellitus and those with beta-cell toxicity caused by an immunosuppressive regimen.

The effect of creatinine clearance on the basal C-peptide level is a limitation in our study. Although the values of creatinine clearance in the kidney transplant alone group and the simultaneous pancreas-kidney transplant group were comparable, the increased half-life of C-peptide in transplant recipients could lead to an overestimation of insulin secretion. Studies that reveal the basal C-peptide values of patients who underwent either kidney transplant alone or a simultaneous pancreas-kidney transplant may be controversial. Some, like the report by Christiansen and colleagues, show higher values in the former (as opposed to the latter) group and in healthy subjects (24), but other investigations suggest that those values are similar in the transplant groups (25). Our results agree with the findings of Christiansen and colleagues (24). Such controversy may be due in part to discrepancies in factors such as kidney allograft function, the immunosuppressive regimen used, and the recipient's age and body mass index. However, the C-peptide level may be a helpful tool for determining HOMA indexes when the specific insulin dosage is not available after transplant.

In our group of patients who underwent kidney transplant alone, prednisone dosages correlated significantly with both HOMA indexes (which suggests that this drug could decrease glucose uptake by peripheral tissues and might contribute to an increase in hepatic gluconeogenesis and a decrease in the glycogen synthesis of skeletal muscle cells). An increase in the insulin sensitivity index after a reduction in the prednisone dosage (26, 27) and reduced insulin-stimulated glucose disposal after the impairment of nonoxidative glucose metabolism are clinical evidence supporting that correlation. (28). Lowering the prednisone dosage also increases the insulin level and C-peptide secretion by beta cells (8).

We are concerned that our patients who underwent kidney transplant alone may fit into stage 1 or stage 2 of the beta-cell dysfunction described by Weir and Bonner-Weir (11). It seems that prednisone may indirectly overstimulate insulin secretion by augmenting insulin resistance. Homeostasis model assessment indexes, therefore, could be used to identify patients with a higher risk for posttransplant diabetes mellitus, even though only a maintenance dose of the corticoid drugs is administered.

Tacrolimus inhibits insulin secretion in a dose-dependent manner; higher levels of tacrolimus are associated with the inhibition of both insulin and C-peptide secretion (8). We expected to find a negative correlation between tacrolimus levels and HOMA of beta-cell function, but that was not the case. The major event, as far as our patients were concerned, was reduced insulin sensitivity, which could explain our findings. In the later stages of beta-cell dysfunction, when insulin sensitivity decreases, HOMA of beta-cell function values decrease as well.

In previous investigations, HOMA values were studied primarily in patients treated with cyclosporine (17). Some studies in which tacrolimus therapy has been implemented have used HOMA model 2 (the computer model of HOMA) in renal transplant recipients (29). Model 2, which should be used only when the results from HOMA are compared with those from other assessment models, reveals variations in hepatic and peripheral glucose resistance. The connection of HOMA 2 and tacrolimus in our study was explained by beta-cell toxicity instead of insulin resistance. Our results excluded cyclosporine-treated subjects, and we evaluated only kidney recipients treated with tacrolimus. In addition, we used HOMA model 1 (the original HOMA), which reflects variations in hepatic glucose resistance and can explain, at least in part, the lack of correlation between HOMA and treatment with tacrolimus.

In our study, the HOMA index and body mass index were correlated in the group that underwent kidney transplant alone. The correlation with insulin sensitivity was reported by others who used a euglycemic-hyperinsulinemic glucose clamp in their study (26). Kidney transplant alone patients were the only subjects in whom we found a positive correlation between the HOMA of beta-cell function and body mass index. That correlation might result from the compensatory overload of beta cells and the subsequent increase in insulin secretion, which can lead to an augmented beta-cell mass or hypertrophy (11). Because of that overload, such patients would benefit from lower dosages of glucocorticoids and associated weight loss.

Homeostasis model assessment in simultaneous pancreas-kidney transplant patients

Data on insulin resistance and sensitivity indexes were poor in the simultaneous pancreas-kidney transplant group. In those patients, the insulin secretion

assessment in which a peripheral C-peptide is used may not be the most accurate. C-peptide values can be affected by creatinine clearance and the systemic delivery of creatinine. Unlike insulin, C-peptide is not removed in by a single pass through the liver. It has been suggested that the most suitable (and laborious) method of evaluating insulin secretion is the analysis of C-peptide kinetics (24).

In a study by Aguilera and colleagues, an oral glucose tolerance test revealed a positive correlation between HOMA of beta-cell function and the lower portion of the insulinemia curve in simultaneous pancreas-kidney transplant recipients (30). Other studies have shown that pancreatic transplant patients exhibit hyperinsulinemia, down-regulation of the number of monocyte insulin receptors, and resistance to the antilipolytic action of insulin (24, 31, 32). Christiansen and colleagues showed that defective insulin secretion can develop in simultaneous pancreas-kidney transplant recipients (24).

In our study, higher dosages of prednisone increased HOMA of beta-cell function values. This suggests that prednisone increases insulin resistance and causes a compensatory increase in insulin secretion in a well-functioning pancreatic allograft. In our kidney transplant alone recipients the HOMA of insulin resistance was greater than that from pancreatic allografts recipients (2.7 vs 2.12, respectively; $P < .0001$; data not shown). However, the overstimulation of beta-cell function could culminate with the exhaustion of those cells. Cumulative dosages of glucocorticoids also contribute to enhanced beta-cell function in patients with rheumatoid arthritis (33).

In contrast to the results of previous reports, our study revealed a negative association of insulin sensitivity with tacrolimus levels (6, 8). Because we included prednisone levels in our analysis, our data might reflect the correlation between higher prednisone dosages and higher tacrolimus levels ($P < .0001$, $r = 0.61$; data not shown). Furthermore, the glucocorticoids may exacerbate the beta-cell injury initiated by calcineurin inhibitors (8). In other words, steroids may override the positive effects of low levels of tacrolimus and may cause persistent insulin resistance (which does not occur in steroid-free patients) (34). The correlation between higher tacrolimus dosages and both higher glucose-stimulated insulin values (35) and a lower insulin sensitivity index has been reported by others (6). In patients with a failing pancreatic allograft, HOMA of

beta-cell function values may gradually decrease as beta-cell dysfunction caused by the cumulative effects of prednisone and tacrolimus progresses.

The association of HOMA of insulin sensitivity with immunosuppressive regimens suggests that insulin sensitivity also may have an important role in the beta-cell function of simultaneous pancreas-kidney transplant patients who have a body mass index within the reference range. However, we believe that if simultaneous pancreas-kidney transplant patients gain a significant amount of weight, then their beta-cell function will eventually be impaired due to decreased insulin sensitivity.

A family history of diabetes in some of our patients was associated with higher values in HOMA of beta-cell function that may be due in part to lower values in the HOMA of insulin sensitivity. To our knowledge, we are the first to report that association in simultaneous pancreas-kidney transplant recipients. Our findings could be explained by the following mechanisms.

First, proportional and reciprocal alteration of insulin output must occur for glucose tolerance to remain constant, even though insulin sensitivity varies. That relation may be described by a hyperbolic function; for example, the quantitative variation of beta-cell function is linked to differences in insulin sensitivity (36). In transplant recipients with lower values of HOMA of insulin sensitivity, beta-cell overstimulation can cause its own exhaustion and can contribute to hyperglycemia over the long term. Other studies (37, 38) have shown that insulin resistance has a major role in the pathophysiology of impaired glucose tolerance. The question of whether insulin sensitivity might have predicted which subject(s) in our study would experience hyperglycemia remains unanswered.

Second, subjects at high risk for type 2 diabetes, such as first-degree relatives of type 2 diabetic individuals, may exhibit beta-cell dysfunction during the first phase of insulin response to intravenous glucose, which is reduced according to the patient's degree of insulin sensitivity (39). Thus beta-cell function is the main determinant of hyperglycemia in first-degree relatives of diabetic patients (40, 41).

Third, subjects in whom type 2 diabetes developed exhibited reduced capability to secrete insulin when insulin sensitivity decreased, but those in whom type 2 diabetes did not develop maintained normoglycemia by the adaptive response of augmenting insulin secretion (41, 42). However, further studies will be

necessary to determine the impact of higher HOMA of beta-cell function values on pancreas allograft survival and beta-cell dysfunction in recipients of a simultaneous pancreas-kidney transplant.

We expected to find a correlation between HOMA of insulin sensitivity values and the administration of angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, because those agents are associated with enhanced beta-cell function. That benefit is probably abrogated by immunosuppressive regimens in transplant recipients (43).

In conclusion, prednisone dosages modified both HOMA indexes in patients who underwent kidney transplant alone and HOMA of beta-cell function values in those who underwent a simultaneous pancreas-kidney transplant. Body mass index was associated with both indexes subjects who underwent kidney transplant alone. Tacrolimus levels changed HOMA of beta-cell function values and HOMA of insulin sensitivity only in recipients of a simultaneous pancreas-kidney transplant, who, if they demonstrated good function of the pancreatic allograft, exhibited lower HOMA of insulin sensitivity values and higher HOMA of beta-cell function values only if there was a family history of diabetes.

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