Circulating Proinsulin Levels in Insulin-Dependent Diabetic Patients After Whole Pancreas-Kidney Transplantation

Tetsuya Babazono, Satoshi Teraoka, Osamu Tomonaga, Yasuhiko Iwamoto, and Yasue Omori

Disproportional hyperproinsulinemia is a sensitive marker for β-cell dysfunction. The objective of this study was to assess the proinsulin profile in persons with insulin-dependent diabetes mellitus (IDDM) after pancreas-kidney transplantation. We determined serum insulin, C-peptide, and proinsulin concentrations during an oral glucose challenge in five pancreas-kidney transplant recipients, nine nondiabetic kidney transplant recipients, and 17 normal subjects. Basal proinsulin concentrations were significantly increased in pancreas-kidney recipients (geometric mean [±1 SE range], 6.0 [5.5 to 6.4] pmol/L) and kidney recipients (6.4 [5.4 to 7.5] pmol/L) compared with the normal subjects (2.8 [2.5 to 3.2] pmol/L). Integrated proinsulin concentrations during the oral glucose load were also higher in pancreas-kidney recipients (1.4 [1.1 to 1.8] nmol/L · min) and kidney recipients (1.5 [1.2 to 2.0] nmol/L · min) versus normal subjects (0.8 [0.7 to 0.9] nmol/L · min). There was no difference in basal or integrated proinsulin concentrations between the two transplant groups. Even after adjustment for the glomerular filtration rate (GFR), basal and incremental proinsulin concentrations continued to be higher in the transplant groups than in the normal subjects. Proinsulin to C-peptide molar ratios both before and after the glucose load were similar in the three groups. From these findings, we conclude that pancreas-kidney transplantation provokes proportional hyperproinsulinemia, which is closely associated with its reduced clearance in the kidneys.

FOLLOWING RECENT ADVANCES in surgical technique and immunosuppressive therapy, pancreas transplantation has become a viable therapeutic modality in selected patients with insulin-dependent diabetes mellitus (IDDM), especially those with end-stage renal disease.[1-4] The International Pancreas Transplant Registry data to date indicate that a total of 7,505 pancreas transplants have been performed worldwide as of November 1995.[1] When technically successful, pancreas transplantation normalizes 24-hour profiles for plasma glucose by restoring self-regulating insulin secretion in persons with IDDM.[5-7] However, several intrinsic and environmental factors have been suggested to affect endocrine function of the pancreatic grafts and glucose metabolism. These include ischemic injury during preservation, overt or subclinical rejection, pancreatic fibrosis, denervation of the allograft, systemic insulin delivery, insulin resistance due to corticosteroids, adverse effects of cyclosporine and tacrolimus (FK506), and impaired renal function.[5-20] Although the metabolic success of pancreas transplantation has been assessed using basal and poststimulated levels of circulating insulin and C-peptide, these tests are considered insufficiently sensitive to determine subclinical abnormalities of pancreatic endocrine function. In addition, peripheral concentrations of insulin or C-peptide alone are limited in their use as a measure of insulin secretion in pancreas transplant recipients.[6,7,21] This is due to the evidence that both reduced hepatic extraction of insulin associated with systemic venous drainage of the pancreatic allografts rather than physiological portal drainage and insulin resistance caused mainly by immunosuppressive drugs induce hyperinsulinemia, and that a reduced glomerular filtration rate (GFR) after simultaneous or prior kidney transplantation curtails the renal clearance of C-peptide, causing increased levels of serum C-peptide.[5-12,14,15,17]

Proinsulin, the precursor of insulin, is secreted to some extent from β cells. Currently, hyperproinsulinemia, especially disproportional hyperproinsulinemia in relation to insulin, is thought to be a sensitive marker for subclinical β-cell dysfunction.[22-26] Furthermore, not only hyperinsulinemia but also hyperproinsulinemia have been suggested to be associated with acceleration of atherosclerosis.[27-30] However, only limited information is available on circulating proinsulin levels in pancreas transplant recipients.[6,15] In the present study, we determined basal and glucose-stimulated levels of circulating proinsulin to assess qualitative β-cell function in persons with IDDM after successful pancreas-kidney transplantation. Because proinsulin, like C-peptide, is cleared mainly by the kidneys,[31,32] impaired renal function in pancreas-kidney recipients may affect serum proinsulin levels. To eliminate this effect, nondiabetic kidney transplant recipients with comparable renal function were also studied as a control group.

SUBJECTS AND METHODS

Subjects

We studied five patients with IDDM after successful pancreas transplantation: three patients received simultaneous pancreas-kidney transplantation and the other two received a pancreatic allograft 14 and 53 months after kidney transplantation (Table 1). They had diabetes for 24 ± 5 years (range, 20 to 32) before pancreas transplantation, and end-stage renal disease requiring dialysis for 35 ± 5 months (range, 30 to 42) before kidney transplantation. All pancreatic grafts were obtained from non–heart-beating cadaveric donors as reported previously.[33] After the donor's cardiac standstill, a whole pancreatic graft and a duodenum were procured and placed onto the recipient's left iliac fossa. A pancreatico-duodeno-cystostomy was performed. Vascular anastomoses were established using iliac vessels, thereby resulting in pancreatic venous drainage into the systemic circulation directly. A kidney graft was transplanted in the right fossa. At the time of the study, both the pancreas and kidney grafts were well functioning; none of the recipients had taken insulin or received dialysis therapy since the respective organ transplantation. They were studied 20 ± 12 months (range, 2 to 34) after pancreas transplantation and 34 ± 29 months (range, 2 to 78) after kidney transplantation. Nine nondiabetic kidney transplant recipients

From the Department of Medicine, Diabetes Center, and Department of Surgery, Kidney Center, Tokyo Women's Medical College, Tokyo, Japan.

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Address reprint requests to Tetsuya Babazono, MD, Diabetes Center, Tokyo Women's Medical College, 8-1 Kawadacho Shinjukuku, Tokyo, 162-8666 Japan.

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Table 1. Clinical Characteristics of the Subjects

Characteristic	Pancreas-Kidney Recipients (n = 5)	Nondiabetic Kidney Recipients (n = 9)	Normal Subjects (n = 17)
Gender (male/female)	1/4	3/6	6/11
Age at test (yr)†	37 ± 5	35 ± 11	29 ± 5
BMI (kg/m²)†	18.2 ± 1.7*	20.3 ± 1.9	21.1 ± 2.0
Serum creatinine (mmol/L)‡	167 (88-317)*	166 (88-315)*	66 (58-75)
Estimated GFR (mL/min)‡	33.9 (17.1-67.4)*	38.7 (18.0-83.4)*	95.2 (85.6-105.8)
Hemoglobin A_{1c} (%)†	4.6 ± 0.8	5.0 ± 0.5*	4.2 ± 0.3
Dosage of immunosuppressive drug (mg/d)†			
Methylprednisolone	8.8 ± 1.8 (n = 5)	9.1 ± 5.5 (n = 9)	—
Cyclosporine	162.5 ± 17.7 (n = 2)	145.0 ± 73.7 (n = 5)	—
Tacrolimus	6.7 ± 1.2 (n = 3)	8.3 ± 4.8 (n = 4)	—
Azathioprine	46.9 ± 15.7 (n = 4)	41.7 ± 14.4 (n = 3)	—
Mizoribine	— (n = 0)	175.0 ± 64.5 (n = 4)	—

Abbreviation: BMI, body mass index.
*$P < .05$ *v* normal subjects.
†Mean ± SD.
‡Geometric mean (± 1 SD range).

were studied as the control group for impaired renal function and immunosuppressive therapy. They were on dialysis for 44 ± 14 months (range, 3 to 80) until transplantation, and were studied 21 ± 19 months (range, 2 to 61) after transplantation. Seventeen individuals with normal glucose tolerance and normal renal function served as a true control group. Informed consent was obtained from all of the subjects.

The three groups of subjects were matched for age and gender (Table 1). The mean body mass index was slightly but significantly lower in pancreas-kidney recipients than in the normal subjects; however, all pancreas-kidney recipients were healthy except for being a transplant recipient and had been free from a rejection episode at least 4 weeks prior to the test. The mean serum creatinine concentrations in the two transplant groups were identical, but were significantly greater than those in the normal subjects. GFR was calculated with the formula recently demonstrated by Nankivell et al[34] to be highly correlated with the Tc^{99m} diethylenetriamine pentaacetic acid (DTPA) GFR in pancreas-kidney transplant patients. The estimated GFRs in the transplant groups were also similar, but were significantly decreased compared with those in the normal subjects. Values for hemoglobin A_{1c} in kidney recipients were slightly but significantly higher than in the normal subjects. All of the transplant recipients were treated with methylprednisolone as the first immunosuppressive drug, and the mean dosage was comparable in the two groups. Either cyclosporine or tacrolimus was selected as the second drug. Both the ratio of patients treated with cyclosporine or tacrolimus and the mean dosage of these drugs were also similar between the two groups. Azathioprine was administered as the third drug in four pancreas-kidney and three kidney recipients. Mizoribine was substituted for azathioprine in four kidney recipients only.

Oral Glucose Tolerance Test and Assays

We performed a standard 75-g oral glucose tolerance test (OGTT) after an overnight fast. Blood samples were drawn immediately before (0 minutes) and 15, 30, 45, 60, 90, 120, and 180 minutes after an oral glucose load for determination of plasma glucose and serum insulin and C-peptide, and 0, 30, 60, 120, and 180 minutes for the serum proinsulin assay. The response to oral glucose was expressed as the area under the curve over the concentration of the time 0 concentration.

The plasma glucose level was measured immediately after the test with a glucose oxidase method using an autoanalyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Serum samples for insulin, C-peptide, and proinsulin assays were stored at −20°C until analysis. Insulin and C-peptide levels were measured using commercially available double-antibody radioimmunoassay kits (insulin, Eiken Chemical, Tokyo, Japan, C-peptide, Shionogi, Osaka, Japan). Both intraassay and interassay variations were less than 5% for insulin and less than 10% for C-peptide. The insulin assay cross-reacted with a human proinsulin standard that contained intact and split forms of proinsulin intermediates by 25% on a molar basis. Serum proinsulin was determined with a radioimmunoassay using recombinant proinsulin-specific antisera (Mitsubishi Kagaku Biochemical Laboratories, Tokyo, Japan) after acid-ethanol extraction. In the proinsulin assay, cross-reactivity with either insulin or C-peptide was less than 0.01%. Split 65,66 proinsulin demonstrated 100% cross-reactivity, whereas split 32,33 proinsulin was much less reactive. This indicates that the antibody used in this assay recognizes a proinsulin-specific epitope formed by the B-chain–C-peptide junction or its vicinity in the proinsulin molecule. Intraassay and interassay coefficients of variation for proinsulin were 5% to 10% and 7% to 18%, respectively. Serum insulin antibodies screened by polyethylene glycol methods[35] were undetectable in all five pancreas-kidney recipients.

Statistical Analysis

Normally distributed data are expressed as the mean ± SD for demographic data and the mean ± SE for results of the OGTT. Positively skewed data were logarithmically transformed to improve the normality for statistical procedures. The mean and mean ± 1 SD (or SE) range of the transformed values were then back-transformed to their natural units for presentation in the tables and figures. We compared categorical data with Fisher's exact test. Continuous data between two groups (dosage of immunosuppressive drug between the two transplant groups) were compared using Student's *t* test. Comparison of continuous data among three groups was made by one-way ANOVA followed by Tukey's studentized range test. In addition, we attempted Spearman's correlation analysis to clarify the relationship between basal or incremental concentrations of pancreatic hormones and other variables.

Because serum C-peptide and proinsulin concentrations are known to increase when renal function is impaired,[31,32] and both transplant groups had decreased renal function as already mentioned, the concentrations of C-peptide and proinsulin before and during the OGTT were also compared using an analysis of covariance (ANCOVA) to adjust for differences in GFR among the three groups. In the ANCOVA, the adjusted geometric mean and back-transformed mean ± SE range were calculated. All of the statistical procedures were performed using Statistical Analysis System (SAS Institute, Cary, NC) version 6.12. A *P* value less than .05 was considered statistically significant.

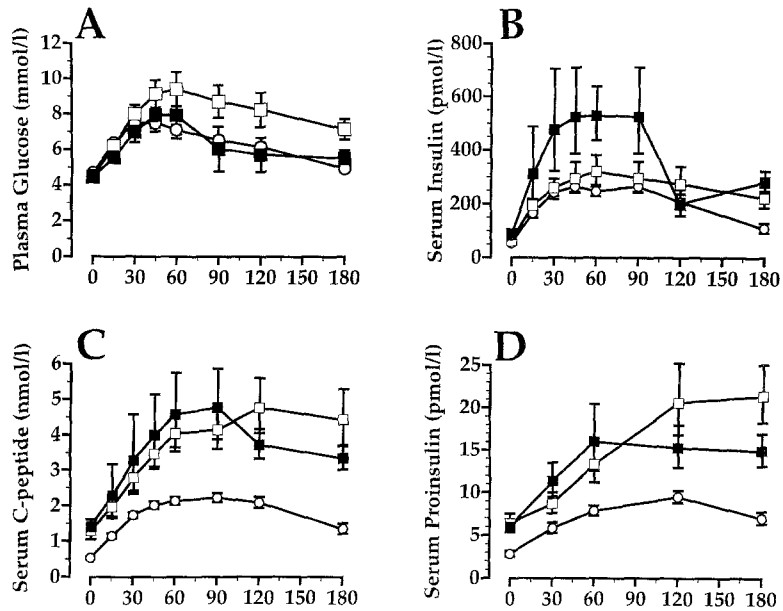

Fig 1. Plasma glucose (A) and serum insulin (B), C-peptide (C), and proinsulin (D) response during 75-g OGTT in 5 pancreas-kidney recipients (■), 7 nondiabetic kidney recipients (□), and 17 normal subjects (○). Data are means ± SE.

RESULTS

Basal plasma glucose levels were similar in the three groups (Fig 1A). Basal insulin levels in pancreas-kidney recipients (geometric mean [± 1 SE range], 84 [67 to 106] pmol/L) were significantly higher than those in the normal subjects (54 [51 to 58] pmol/L), but did not differ from the levels in kidney recipients (63 [57 to 69] pmol/L; Figure 1B). Basal C-peptide concentrations in pancreas-kidney recipients (1.41 [1.34 to 1.48] nmol/L) and kidney recipients (1.30 [1.05 to 1.62] nmol/L) were significantly higher than in the normal subjects (0.54 [0.50 to 0.58] nmol/L; Figure 1C). Basal proinsulin concentrations were also significantly increased in pancreas-kidney recipients (6.0 [5.5 to 6.4] pmol/L) and kidney recipients (6.4 [5.4 to 7.5] pmol/L) compared with the normal subjects (2.8 [2.5 to 3.2] pmol/L; Fig 1D). There was no significant difference in basal C-peptide or proinsulin levels between the transplant groups.

Although both transplant groups showed a delayed response of plasma glucose, the integrated plasma glucose concentrations after the glucose load in pancreas-kidney recipients (232.2 [143.6 to 375.8] mmol/L · min) were not significantly different, but were even lower than those in the normal subjects (281.9 [261.1 to 304.3] mmol/L · min), whereas the concentrations were significantly higher in kidney recipients (532.1 [419.1 to 675.5] mmol/L · min) than in the other two groups (Fig 1A). A greater response of serum insulin was observed in pancreas-kidney recipients (Fig 1B). The area under the insulin curve in pancreas-kidney recipients (50.1 [36.5 to 68.7] nmol/L · min) was greater than in kidney recipients (36.9 [31.4 to 43.4] nmol/L · min) and in the normal subjects (27.6 [25.0 to 30.6] nmol/L · min). Because the insulin response in the three groups was highly variable even after logarithmic transformation, marginal statistical significance was found only between the pancreas-kidney recipients and normal subjects ($P = .07$). Both C-peptide and proinsulin concentrations during the OGTT in pancreas-kidney recipients (C-peptide, 423.2 [331.4 to 540.4] nmol/L · min; proinsulin, 1.4 [1.1 to 1.8] nmol/L · min) and kidney recipients (453.7 [397.8 to 517.5] nmol/L · min, 1.5 [1.2 to 2.0] nmol/L · min) were markedly and significantly higher than in the normal subjects (228.9 [213.2 to 245.8] nmol/L · min; 0.8 [0.7 to 0.9] nmol/L · min; Fig 1C and D). There was no difference in integrated C-peptide or proinsulin levels between the transplant groups.

In the basal state, the proinsulin to insulin molar ratio in pancreas-kidney recipients did not increase, but the ratio increased significantly in kidney recipients compared with the normal subjects (Table 2). The proinsulin to insulin molar ratio of the incremental concentration was identical in pancreas-kidney recipients and normal subjects (Table 2). There were no significant differences in the proinsulin to C-peptide molar ratio either before or after the glucose load among the three groups (Table 2).

Spearman's correlation analyses showed that serum creatinine and the estimated GFR were strongly related to serum C-peptide and proinsulin concentrations both before and during the OGTT (Tables 3 and 4). The integrated proinsulin concentration and its molar ratio to C-peptide were also significantly correlated with the integrated glucose concentration (Table 4).

After adjustment for the GFR by ANCOVA, the geometric mean concentrations of basal C-peptide and proinsulin continued to be higher in pancreas-kidney recipients versus normal subjects, with statistical significance ($P = .03$) for C-peptide and marginal significance ($P = .142$) for proinsulin, but were almost identical to the corresponding values in kidney recipients (Table 2). The integrated C-peptide and proinsulin levels adjusted for GFR also tended to be higher in both transplant groups than in the normal subjects, although the differences did not reach statistical significance (Table 2).

DISCUSSION

In the current study, we have shown that pancreas-kidney transplantation causes an elevation of not only insulin and C-peptide but also proinsulin levels both before and during an oral glucose challenge. We have also demonstrated almost

Table 2. GFR-Adjusted Basal and Integrated Concentrations of Serum C-peptide and Proinsulin and Molar Ratio of the Three Pancreatic Hormones

Parameter	Pancreas-Kidney Recipients (n = 5)	Nondiabetic Kidney Recipients (n = 9)	Normal Subjects (n = 17)
Basal concentration			
Molar ratio (%)			
Proinsulin/insulin	7.1 (5.5-9.1)	10.1 (9.0-11.5)*	5.2 (4.6-5.8)
Proinsulin/C-peptide	0.42 (0.38-0.46)	0.49 (0.44-0.53)	0.52 (0.47-0.58)
GFR-adjusted concentration			
C-peptide (nmol/L)	1.13 (0.94-1.37)*	1.09 (0.95-1.25)*	0.64 (0.57-0.71)
Proinsulin (pmol/L)	5.0 (4.0-6.3)	5.5 (4.7-6.6)*	3.2 (2.8-3.7)
Integrated concentration			
Molar ratio (%)			
Proinsulin/insulin	2.9 (2.5-3.2)	4.2 (3.4-5.3)	2.8 (2.4-3.2)
Proinsulin/C-peptide	0.34 (0.31-0.37)	0.34 (0.29-0.40)	0.34 (0.30-0.38)
GFR-adjusted concentration			
C-peptide (nmol/L · min)	373.3 (311.2-447.8)	411.4 (358.7-471.8)*	250.2 (225.1-278.1)
Proinsulin (nmol/L · min)	1.25 (0.91-1.72)	1.40 (1.10-1.77)	0.84 (0.70-1.02)

NOTE. Data are the geometric mean (± 1 SE range).

*$P < .05$ *v* normal. GFR-adjusted values were calculated and compared using ANCOVA. Molar ratios were compared by ANOVA following Tukey's studentized range test.

identical responses of both C-peptide and proinsulin in pancreas-kidney recipients and nondiabetic kidney recipients. Because C-peptide and proinsulin are known to be cleared primarily by the kidneys, and because proinsulin levels were found to be directly correlated with renal function in this and previous studies,[15,31] our data strongly suggest that increased proinsulin levels in pancreas-kidney recipients are mainly due to its reduced clearance. However, even after adjustment for GFR, both the pancreas-kidney and kidney recipients continued to have higher proinsulin levels, suggesting that increased secretion from the β cells could also contribute to hyperproinsulinemia.

Whether proinsulin in pancreas-kidney recipients increases proportionately or disproportionately in relation to insulin is of great importance, because the latter type of hyperproinsulinemia rather than absolute hyperproinsulinemia itself has been implicated as an early marker for β-cell dysfunction.[23,25,26] However, systemic venous drainage of the pancreatic allograft and impaired renal function restrict the use of peripheral insulin or C-peptide and proinsulin concentrations as a measure of insulin and proinsulin secretory function of the pancreatic graft.[6,7,21] Under these circumstances, molar ratios of proinsulin to C-peptide instead of insulin seem suitable to assess the relative secretion rate of proinsulin to insulin because hepatic extraction of C-peptide and proinsulin is negligible. In the current study, we found no significant differences in the proinsulin to C-peptide molar ratio both basally and during the OGTT among the three groups, suggesting proportional hyperproinsulinemia in both pancreas-kidney and nondiabetic kidney recipients.

Whereas the proinsulin to C-peptide molar ratio provides information only on the relative secretion rate of proinsulin to insulin, proinsulin and C-peptide concentrations adjusted for GFR could be used as an unsophisticated measure of respective proinsulin and insulin secretion in persons with a range of

Table 3. Spearman's Correlation Coefficients Between Basal Concentrations of Pancreatic Hormones and Other Variables

Variable	Insulin	C-Peptide	Proinsulin	Proinsulin/ Insulin	Proinsulin/ C-Peptide
Serum creatinine	.301	.699‡	.718‡	.562‡	−.212
Estimated GFR	−.308	−.705‡	−.683‡	−.511†	.281
Hemoglobin A_{1c}	.061	.376*	.252	.196	−.403*
MP dosage	.005	.383	.606*	.471	−.137
Basal glucose	−.029	−.336	−.292	−.274	.039
Basal insulin	—	—	.483†	—	—
Basal C-peptide	.697‡	—	.828‡	—	—

NOTE. All variables other than MP dosage were analyzed in all subjects (n = 31). MP dosage was analyzed only in transplant recipients (n = 14).

Abbreviation: MP, methylprednisolone.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Table 4. Spearman's Correlation Coefficients Between Integrated Concentrations of Pancreatic Hormones and Other Variables

Variable	Insulin	C-Peptide	Proinsulin	Proinsulin/ Insulin	Proinsulin/ C-Peptide
Serum creatinine	.209	.714‡	.502†	.220	−.058
Estimated GFR	−.323	−.697‡	−.432*	−.100	.058
Hemoglobin A_{1c}	.185	.575‡	.441*	.188	.045
MP dosage	.061	.207	.237	.460	.182
Basal glucose	−.219	−.094	−.170	.093	.022
Basal insulin	.323	.277	.001	−.306	−.227
Basal C-peptide	.473†	.590‡	.386*	−.029	−.070
Integrated glucose	.180	.437*	.522†	.449*	.423*
Integrated insulin	—	—	.498†	−.266	.046
Integrated C-peptide	.657‡	—	.743‡	.162	.071

NOTE. All variables other than MP dosage were analyzed in all subjects (N = 31). MP dosage was analyzed only in transplant recipients (n = 14).

Abbreviation: MP, methylprednisolone.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

GFRs. Thus, higher adjusted concentrations of proinsulin and C-peptide and a normal proinsulin to C-peptide ratio, both of which were observed in the transplant groups, suggest that insulin and proinsulin secretion increased in parallel, leading to proportional hyperproinsulinemia. Hypersecretion of insulin associated with hepatic and peripheral insulin resistance is believed to be, in part, attributable to hyperinsulinemia in pancreas transplantation.[10,11,14,19,20] In addition to immunosuppressive treatment, systemic insulin delivery,[36] chronic hyperinsulinemia itself,[37] and impaired renal function,[38] all of which are associated with pancreas-kidney transplantation, lead to insulin resistance. Hyperproinsulinemia also occurs when insulin resistance exists[39,40]; however, its relation to hyperinsulinemia seems controversial. Insulin resistance in simple obesity causes absolute and proportional hyperproinsulinemia unless there is hyperglycemia.[39] On the other hand, dexamethasone-induced acute insulin resistance has been reported to produce disproportionate hyperproinsulinemia in normal subjects.[40] However, the higher biological potency and acute effects of glucocorticoids may be responsible for the increase in the proinsulin to insulin ratio, because basal plasma glucose levels after dexamethasone treatment in the previous study were significantly higher than the pretreatment levels.[40] In our study, pancreas-kidney recipients had normal levels of plasma glucose both before and after the oral glucose load, which may be due to long-term administration of less potent glucocorticoids, presumably associated with proportional hyperproinsulinemia. Thus, it is likely that relative proinsulin concentrations depend on the degree of hyperglycemia caused by insulin resistance.

In contrast to our results, Christiansen et al[6] demonstrated higher fasting and postprandial proinsulin to C-peptide ratios in segmental pancreas-kidney recipients versus nondiabetic kidney recipients and normal subjects. This discrepancy may arise from the different quantity of β-cell mass transplanted with whole versus segmental pancreatic grafts. A near-normal response of plasma glucose was observed in our whole pancreas-kidney recipients, whereas segmental pancreas recipients in the previous study exhibited an increased postprandial glycemic response compared with kidney recipients.[6] Therefore, disproportionate hyperproinsulinemia observed in the segmental pancreas recipients is most likely attributable to the reduced β-cell mass, which is not enough to compensate for an enhanced demand for insulin. Supporting this is the finding that disproportionate hyperproinsulinemia accompanied by glucose intolerance occurs in healthy subjects after hemipancreatectomy for the purpose of graft donation.[26]

In conclusion, whole pancreas-kidney transplantation induces not only hyperinsulinemia but also hyperproinsulinemia before and during an OGTT. An increased proinsulin concentration in pancreas-kidney transplant recipients is closely associated with its reduced clearance in the kidneys and may also be due, in part, to hypersecretion of this prohormone in parallel with insulin, suggesting proportional hyperproinsulinemia that is less indicative of allograft β-cell dysfunction. Whether the absolute hyperproinsulinemia contributes to acceleration of atherosclerosis[27-30] should be determined in a long-term follow-up study.

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