Quality of life in Japanese patients with type 1 diabetes and end-stage renal disease undergoing simultaneous pancreas and kidney transplantation

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Abstract We conducted this cross-sectional study to assess quality of life (QOL) in Japanese patients with type 1 diabetes mellitus (T1DM) and end-stage renal disease (ESRD) undergoing simultaneous pancreas and kidney transplantation (SPK). Japanese patients with T1DM without diabetic nephropathy ($N = 10$), and those undergoing chronic dialysis ($N = 52$), kidney transplantation alone (KTA, $N = 25$), and SPK ($N = 16$) were studied. Comprehensive health-related QOL was assessed using the Short Form 36 version 2 (SF-36v2). Emotional functioning in diabetes was measured by the Problem Area In Diabetes (PAID) scale. Severity of impaired hypoglycemic awareness was assessed using the Clarke hypoglycemic score. SPK patients had significantly higher (or tended to have higher) subscale and summary SF-36 scores than dialysis patients and KTA patients. PAID scores were significantly lower in SPK patients than in dialysis patients and KTA patients. Clarke hypoglycemic scores were also significantly lower in SPK patients than dialysis patients. In KTA and dialysis patients, there were no significant differences in the SF-36 subscale/summary scores, PAID scores, or Clarke hypoglycemic scores. In conclusion, QOL for Japanese patients receiving SPK may be superior to that of

dialysis patients and KTA patients. Whether SPK actually improves QOL needs to be clarified in longitudinal studies.

Keywords Type 1 diabetes mellitus · Pancreas transplantation · SF-36 · PAID scores · Clarke scores

Introduction

Pancreas transplantation is still the only therapy available for restoring insulin secretion and glycemic control in type 1 diabetes mellitus (T1DM). According to the International Pancreas Transplant Registry, more than 37,000 pancreas transplantations have been performed worldwide as of 2010 [1]. While organ donation is less common in Japan than in other countries, the annual number of pancreas transplants has risen to approximately 30 since the revised Organ Transplant Law went into effect in 2010. A total of 255 patients with T1DM have received pancreas transplantation as of May 2016 [2]. In terms of long-term clinical effectiveness, pancreas transplantation has been shown to prevent the progression of diabetic neuropathy, retinopathy, nephropathy in both original kidneys and transplanted kidneys, and macroangiopathy [3–5], as well as to prolong patient survival [6, 7].

Effects of pancreas transplantation on quality of life (QOL) have also been addressed in depth. The most common category of pancreas transplantation [1] is pancreas transplantation performed simultaneously with kidney transplantation [1, 2]. However, given that kidney transplantation can improve QOL [8], it is still unclear whether simultaneous pancreas and kidney transplantation (SPK) yields an additional benefit for QOL compared to kidney transplantation alone (KTA) [9–13]. Further, it is unclear whether or to what extent the disappearance of anxiety over

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the fear of hypoglycemia and the normalization of glycemia after pancreas transplantation contributes to the improvement of QOL after pancreas transplantation in patients with T1DM. We therefore conducted this study to compare patients with T1DM and ESRD who were undergoing SPK to patients without diabetic nephropathy, those treated with dialysis, and those undergoing KTA in terms of health-related QOL (HRQOL) and hypoglycemia severity.

Subjects and methods

Subject selection

This was a hospital-based cross-sectional study of Japanese adult patients with T1DM. Subjects were recruited from ambulatory patients at the Diabetes Center, Tokyo Women's Medical University Hospital, Tokyo, Japan, during the period between February 2013 and May 2014. A total of 109 patients agreed to participate in this study. There were 74 women and 35 men, and the mean age ($\pm$ standard deviation) was 45 ± 8 years. Of those 109 patients, 16 patients had preneuropathy, defined as an estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m² and urinary albumin excretion of less than 30 mg/g creatinine, according to the Classification of Diabetic Nephropathy 2014 [14], proposed by the Joint Committee on Diabetic Nephropathy. Among the remaining patients, 25, 58, and 10 patients were undergoing chronic dialysis, KTA, and SPK, respectively. Only SPK and KTA patients who had a functioning pancreas and/or kidney grafts were studied. SPK patients were excluded if they resumed insulin therapy after transplantation due to pancreas graft malfunction ($N = 8$). SPK and PTA patients were excluded if they resumed dialysis due to kidney graft failure ($N = 10$). Those undergoing secondary transplantation were also excluded.

This study was performed with the consent of the subjects and based on the Declaration of Helsinki II. Maximum effort was expended to protect the subjects' privacy and other rights.

Evaluation of QOL

To evaluate QOL, we used (1) Medical Outcome Health Survey Short Form 36 version 2 (SF-36v2) [15], (2) the Problem Areas in Diabetes (PAID) scale [16], and (3) the Clarke hypoglycemic score [17]. SF-36v2 is a nonspecific method of evaluating overall HRQOL; the latter two are disease-specific scales. All of these were self-administered surveys. SF-36 consists of 8 subscales, the scores of which were entered into the scoring program and normalized based on the 2007 reference values for the Japanese populace to obtain a mean of 50 points and a SD of 10 points. The

subscales of SF-36 were: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. The scores of these 8 subscales were then used to calculate the following three summary scores: the physical component summary score, mental component summary score, and role-social component score. The reliability of the Japanese version of the SF-36v2 was validated previously [15].

The PAID scale uses 20 questions to evaluate psychological distress from diabetes and its treatment. Severe psychological distress was defined as a PAID score of 50 points or higher [16]. The Clarke hypoglycemic score, consisting of 8 questionnaire items, was used to assess severity of hypoglycemic awareness. Increased risk of hypoglycemic unawareness was defined as a Clarke hypoglycemic score of 4 or higher [17].

Clinical examination data

Laboratory data were obtained from the hospital medical records, using the results closest (normally within 7 days) to the date when the above questionnaires were administered. Glycated hemoglobin (HbA1c) and serum glycated albumin (GA) levels were measured by high-performance liquid chromatography and serum creatinine was determined by an enzymatic method. eGFR was calculated using the Japanese Society of Nephrology's formula for estimating eGFR in Japanese people [18]: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine (mg/dL)}^{-1.094} \times \text{age (years)}^{-0.287}$ ($\times 0.739$ for women).

Statistical analysis

Continuous variables were expressed as the arithmetic mean $\pm$ SD or median value (interquartile range). Between-group comparisons of continuous variables in two groups were conducted with Student's *t* test. Comparisons of continuous variables among three or more groups were conducted using one-way analysis of variance or the Kruskal–Wallis test, followed by the Tukey–Kramer test for multiple comparisons. Discrete variables were compared with Fisher's exact probability test and Juneau's nonparametric multiple comparison test [19]. All statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA). *p* values of less than 0.05 were considered to indicate statistical significance.

Results

Table 1 shows the clinical and laboratory data for patients with T1DM according to the stage of nephropathy and the therapeutic modality for ESRD. There were no differences

Table 1 Clinical characteristics and laboratory data of patients with type 1 diabetes according to stage of nephropathy and therapeutic modality for end-stage renal disease

	Prenephropathy (<i>N</i> = 10)	End-stage renal disease			<i>p</i> value
		Dialysis (<i>N</i> = 58)	KTA (<i>N</i> = 25)	SPK (<i>N</i> = 16)	
Current age (years)	44.2 ± 8.6	44.7 ± 8.0	45.2 ± 8.0	45.8 ± 4.9	NS
Male (%)	30.0	32.8	20.0	50.0	NS
Age at onset of diabetes (years)	18.2 ± 11.7	15.3 ± 6.9	16.2 ± 8.3	13.2 ± 7.9	NS
Duration of dialysis (years)	–	7.8 ± 5.8	2.8 ± 3.2	8.9 ± 3.6	<0.001
Duration of diabetes (years)	26.0 ± 9.8	29.3 ± 8.1	28.9 ± 7.2	32.6 ± 5.2	NS
Post-transplant duration (years)	–	–	4.6 ± 3.6	3.5 ± 3.4	NS
Insulin dosage (units/day)	42 ± 14	27 ± 9	33 ± 10	–	<0.001
HbA1c (%)	8.9 ± 1.4	8.0 ± 1.4	8.3 ± 1.3	5.5 ± 0.3	<0.001
Glycated albumin (%)	26.4 ± 2.6	29.7 ± 8.2	26.5 ± 5.4	14.6 ± 1.3	<0.001
Hemoglobin (g/dL)	13.1 ± 2.3	11.6 ± 0.9	12.0 ± 1.6	12.7 ± 2.2	0.015
Albumin (g/dL)	4.0 ± 0.5	3.9 ± 0.4	4.3 ± 0.3	4.1 ± 0.5	0.034
Serum creatinine (mg/dL)	0.72 ± 0.12	9.3 ± 2.4	1.35 ± 0.44	1.06 ± 0.32	<0.001
eGFR (mL/min/1.73 m ²)	74.1 ± 13.1	4.9 ± 1.5	43.0 ± 18.0	57.6 ± 14.9	<0.001

Data are expressed as the percentage or mean ± standard deviation (SD). Categorical data were compared using Fisher's exact probability test and continuous data were compared by one-way ANOVA or Student's *t* test

HbA1c hemoglobin A1c, *KTA* kidney transplantation alone, *SPK* simultaneous pancreas and kidney transplantation

in terms of age at the time of the survey, age at diabetes onset, gender, or diabetes duration. The KTA patients had the shortest dialysis vintage among the three ESRD groups. Of the dialysis patients, 55 and 3 were undergoing hemodialysis and peritoneal dialysis, respectively. HbA1c and serum GA levels were within the normal range and were significantly lower in the SPK group. The post-transplant observational period did not differ significantly between the two transplant groups. In the KTA group, 25 patients received a kidney graft from a living donor and the other patient received it from a deceased donor. In contrast, all of the SPK patients received both pancreas and kidney grafts from a deceased donor ($p < 0.001$).

Figure 1 shows comparisons of 8 subscale scores of SF-36 and Fig. 2 compares the summary scores among the four groups. Overall, the dialysis patients and KTA patients tended to have lower subscale scores than the preneuropathy patients, and the SPK patients tended to have higher subscale scores than the dialysis patients and KTA patients. No differences were observed between the dialysis and KTA patients on any subscale. Among the SF-36 summary scores, physical and mental component scores were significantly higher in the SPK patients than the dialysis patients (Fig. 2), while no differences in role-social component scores were found in the four groups.

Next, we examined the PAID scores, which indicate the level of diabetes-specific emotional distress experienced by a patient (Table 2). The score was significantly lower in the SPK patients than in the other three groups. The number of patients with scores of 50 points or higher, indicating

severe distress from diabetes, was significantly smaller in the SPK group than in the dialysis and KTA groups, but was similar for the preneuropathy and SPK groups.

Lastly, we examined the Clarke hypoglycemic scores, which assess risk of hypoglycemic unawareness (Table 2). The Clarke score for the SPK patients was significantly lower than that for the dialysis patients but was not significantly different from the Clarke scores for the preneuropathy patients and KTA patients. The proportion of patients at high risk of hypoglycemic unawareness, defined as a score of 4 or higher, was lower in the SPK group than the dialysis group. The proportions for the KTA and SPK groups were significantly lower than that for the dialysis group. There was no significant difference between the groups with preneuropathy and KTA, between the groups with preneuropathy and SPK, or between the two transplant groups in terms of the proportion of patients at high risk of hypoglycemic unawareness.

Discussion

In this cross-sectional study, we compared the QOL in Japanese patients with T1DM undergoing SPK with the QOL in patients who did not have diabetic nephropathy, in patients who were treated with chronic dialysis, and in patients who had undergone KTA, with the goal of estimating the effects of SPK on the QOL. The results showed that SPK patients were likely to have higher scores for the overall HRQOL as assessed by SF-36 than dialysis

Fig. 1 Comparison of subscale scores of the SF-36 using norm-based scoring. *KTA* kidney transplantation alone, *SPK* simultaneous pancreas–kidney transplantation. § $p < 0.05$ versus normal group, * $p < 0.05$ versus dialysis group, † $p < 0.05$ versus *KTA* group

Fig. 2 Comparison of summary scores of the SF-36 using norm-based scoring. *KTA* kidney transplantation alone, *SPK* simultaneous pancreas–kidney transplantation, *PCS* physical component summary,

MCS mental component summary, *RCS* role-social component summary. § $p < 0.05$ versus normal group, * $p < 0.05$ versus dialysis group, † $p < 0.05$ versus *KTA* group

patients. SPK patients also exhibited better PAID scores and Clarke hypoglycemic scores than dialysis patients, indicating that SPK patients experienced less psychological distress from diabetes and tended to be more aware of hypoglycemia. When compared to KTA, SPK did not yield significant differences in the SF-36 subscale scores or summary scores or in hypoglycemia severity, but it did decrease the psychological stress from diabetes. These findings suggest that SPK is associated with improved QOL when compared to dialysis and KTA in patients with T1DM and ESRD.

Studies from the United States and European countries indicate that SPK is associated with higher physical component summary scores but not mental component summary scores as well as with less psychological distress from diabetes [8, 20]. In contrast, studies from Japan found an improvement in both physical and mental functioning after SPK, similar to our results [11–13]. Thus, the effects of SPK on the QOL varies between studies. The reason for this is unclear; however, we believe that the length of the waiting period until SPK may affect mental functioning after SPK. In the United States and European countries, the

Table 2 Comparison of PAID and Clarke scores in patients with type 1 diabetes according to stage of nephropathy and therapeutic modality for end-stage renal disease

	Prenephropathy (<i>N</i> = 10)	End-stage renal disease			<i>p</i> value		
		Dialysis (<i>N</i> = 58)	KTA (<i>N</i> = 25)	SPK (<i>N</i> = 16)	Versus prenephropathy	Versus dialysis	Versus KTA
PAID score							
Median (IQR)	44 (34–54)	62 (47–69)	51 (35–60)	26 (21–35)	0.038	<0.001	0.002
≥50 (%)	40.0	69.9	56.0	7.1	0.223	<0.001	0.016
Clarke score							
Median (IQR)	2.5 (0–3.3)	3 (2–5)	2 (1–3)	1 (0–2)	0.69	<0.001	0.21
≥4 (%)	30.0	47.3	16.0	6.3			

waiting period ranged from just 1.1 to 2.0 years [21], whereas the mean waiting period was 8.9 years among the SPK patients in the present study. Whether the improvement in mental component summary scores observed in the present study was likely associated with the prior waiting period needs to be clarified in future studies.

When the SPK and KTA patients were compared, their physical or mental component summary scores did not differ significantly. SPK may lead to better physical component summary scores due to improvements in surgical techniques, advances in immunosuppressive therapies and management of complications, and marked improvements in the patient survival rate and pancreas/kidney graft survival rates [1]. Moreover, as for the improvement in mental summary scores in SPK patients, KTA is unlikely to remove the worry caused by daily hypoglycemia in patients with T1DM, and the KTA patients in this study included those also waiting for pancreas transplantation, presumably leading to a lack of satisfaction with having had only a kidney transplant. On the other hand, SPK may have a negative impact on the QOL because of the difficulty associated with the surgical technique, a higher re-operation rate than KTA, more frequent postoperative complications associated with a pancreas graft (including graft pancreatitis), and longer hospital stays [22]. Indeed, in the current study, 6 patients undergoing SPK required re-operation due to postoperative surgical complications, including venous thrombosis, leak, hemorrhage, or dehiscence. In contrast, only 1 patient underwent reoperation after KTA, due to dehiscence. Moreover, the mean length of hospitalization was 57 days among the SPK patients (data not shown). Since these factors may impact the QOL, it is still unclear whether SPK yields better QOL than KTA [8, 20]. The present study did not investigate which factors improved or worsened the QOL in individual patients, and thus this topic requires further investigation.

The PAID score, a measure of satisfaction with diabetes therapy, was lower in the SPK group than in the other three groups. The reasons for this may include the fact that

frequent insulin injections and self-monitoring of blood glucose levels were no longer necessary after successful pancreas transplantation, and that patients no longer had to worry about symptoms of both hyperglycemia and hypoglycemia, especially in those experiencing frequent episodes of hypoglycemic unawareness. This was supported by the findings that the risk of hypoglycemic unawareness evaluated using the Clarke score was, as expected, very low in SPK patients who had halted insulin therapy. For patients with T1DM, hypoglycemia has a large impact on the QOL [23]. In particular, patients with both T1DM and ESRD are known to be at a much higher risk of experiencing severe hypoglycemia due to impaired secretion of counterregulatory hormones, including glucagon and catecholamines [24, 25], as well as decreased renal gluconeogenesis [26]. Previous studies that examined the QOL in SPK patients [9–13] did not investigate the effects of hypoglycemia on the QOL. As we previously suggested, the ability of patients with T1DM treated with chronic dialysis or KTA to recover from hypoglycemia reversed after SPK as the counterregulatory hormone response to hypoglycemia was normalized [24].

The Clarke hypoglycemic scores of the SPK patients demonstrated that hypoglycemic episodes may persist even after the withdrawal of insulin. In fact, some SPK patients experienced postprandial reactive hypoglycemia. This is likely due to the following intrinsic and environmental factors that may affect the endocrine function of the pancreatic graft: hyperinsulinemia associated with current surgical procedures delivering endogenous insulin from the graft into the systemic circulation, bypassing the portal system; decreased insulin clearance from the implanted kidney; and denervation of the graft. Nonetheless, the lower Clarke scores suggested that hypoglycemic symptoms were mild enough to be self-managed.

When comparing the QOL in the KTA and dialysis groups, we did not find any differences in the SF-36 subscale scores, PAID scores, or Clarke scores, suggesting that KTA is unlikely to improve the QOL in patients with

T1DM and ESRD undergoing chronic dialysis. In contrast, previous studies have shown that, regardless of the presence of diabetes, QOL improves when patients are released from the constraints of dialysis therapy after kidney transplantation [8, 27]. In studies from other institutions in Japan [11], KTA patients exhibited a QOL that was around the same level of that of dialysis patients and reported that they did not feel physically or mentally better after they had received a kidney transplantation, similar to our findings. The reason for this is unclear; however, as described above, it is possible that some of KTA patients desired a pancreas transplant after receiving a kidney transplant or were worried about going back on dialysis owing to the recurrence of diabetic nephropathy in the transplanted kidney. Other forms of emotional instability may also have played a role, such as the threat of rejection or the need to take immunosuppressive agents including glucocorticoids for long periods of time.

Our study has several limitations. First, this was a single-center study from Japan, limiting the generalizability of the present findings. Second, the number of patients (especially those with preneuropathy) may be insufficient to yield definitive conclusions. Third, this was a cross-sectional study; therefore, to further clarify the effects of SPK on the QOL, identical patient groups should be compared before and after SPK, and comparisons should be made after SPK between patients with a functioning graft and those with a rejected graft. Fourth, we were unable to obtain data on blood pressure and the use of antihypertensive agents.

In conclusion, this cross-sectional study suggests that Japanese patients with T1DM after successful SPK have a better QOL than those undergoing dialysis, are likely to be highly satisfied with the therapeutic modality, and are at an extremely low risk of unconscious hypoglycemia. Prospective studies including a larger number of subjects need to be performed to clarify if SPK actually improves QOL in patients with T1DM and ESRD.

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Compliance with ethical standards

Conflict of interest All of the authors declare that they have no conflict of interest.

Human rights statement and informed consent This study was performed with the consent of the subjects and was based on the Declaration of Helsinki II. Maximum effort was expended to protect the subjects' privacy and other rights.

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