Simultaneous pancreas and kidney transplantation as the standard surgical treatment for diabetes mellitus patients with end-stage renal disease

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ABSTRACT

Objectives: To review the outcome following simultaneous pancreas and kidney transplantation in patients with type 1 diabetes mellitus and end-stage renal disease, as well as those with type 2 diabetes mellitus, and to discuss the applicability of this treatment in this locality.

Methods: A systematic literature review was performed by searching the PubMed and Elsevier databases. The search terms used were "simultaneous pancreas and kidney transplantation", "diabetes", "pancreas transplant" and "SPK". Original and major review articles related to simultaneous pancreas and kidney transplantation were reviewed. Papers published in English after 1985 were included. Clinical outcomes following transplantation were extracted for comparison between different treatment methods. Outcomes of simultaneous pancreas and kidney transplant and other transplantation methods were identified and categorised into patient survival, graft survival, diabetic complications, and quality of life. Patient survivals and graft survivals were also compared.

Results: Currently available clinical evidence shows good outcomes for type 1 diabetes mellitus in terms of patient survival, graft survival, diabetic complications, and quality of life. For type 2 diabetes mellitus, the efficacy and application of the procedure remain controversial but the outcomes are possibly comparable with those in type 1 diabetes mellitus.

Conclusions: Simultaneous pancreas and kidney transplantation is a technically demanding procedure that is associated with significant complications, and it should be regarded as a 'last resort' treatment in patients whose diabetic complications have become life-threatening or severely burdensome despite best efforts in maintaining good diabetic control through lifestyle modifications and medications.

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Introduction

Simultaneous pancreas and kidney transplantation (SPK) has emerged as the worldwide standard for treatment of patients with end-stage renal disease (ESRD) resulting from type 1 diabetes mellitus (T1DM). Multiple studies have shown that SPK can significantly improve both their quality of life (QOL) and long-term survival. With the advances in surgical techniques, immunosuppression, management of graft rejection, and other related complications, SPK can now be performed successfully in the majority of patients, with the pancreatic graft survival rate comparable with those of kidney and liver transplants.[1] It is currently the predominant type of pancreas transplantation for diabetic patients with ESRD.[2] According to the International Pancreas Transplant Registry, among over 35 000 pancreas

transplantations reported by the end of 2010, approximately 75% were SPK, 18% were pancreas after kidney transplantation (PAK), and 7% were pancreas transplantation alone.[2] The vast majority of SPK performed in various countries used grafts from cadavers, while living donor pancreas and/or kidney grafts were used only in a minority of cases.

In this review, we first discuss the effectiveness of SPK in improving the outcome for diabetic patients with ESRD in comparison with other transplant options including kidney transplant alone (KTA). In addition, we address the controversy about whether patients with type 2 diabetes mellitus (T2DM)–associated ESRD, as with T1DM patients, should also receive SPK. This is followed by a discussion on the surgical risks, operative complications, future directions, and the application of this treatment

approach in this locality. We reviewed original and review articles related to SPK. PubMed and Elsevier databases were searched using the keywords "simultaneous pancreas and kidney transplantation", "diabetes", "pancreas transplant", and "SPK". Articles published in English since 1985 were included.

Outcomes of type 1 diabetes with end-stage renal disease following simultaneous pancreas and kidney transplantation versus kidney transplant alone (living or deceased donor)

The outcomes of SPK can be assessed in terms of patient survival, graft survival, control of diabetic complications, and improvement in QOL. In the following, comparisons with KTA are made.

Patient survival

The most important parameter is patient survival. Lindahl et al[3] reviewed 15 studies that compared the survival outcomes of SPK, living donor kidney alone (LDKA), and deceased donor kidney alone (DDKA). The authors included nine studies with short-term (up to 10 years) and six studies with long-term (beyond 10 years) follow-up (Table 1[4-19]; one more latest short-term study in 2015 was included[19]). Overall, most large-scale studies agree that DDKA is inferior to SPK and LDKA. Nonetheless, whether

胰腎聯合移植作為糖尿病患者末期腎病的標準手術療法

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目的：分析曾接受胰腎聯合移植的一型糖尿病末期腎病患者的結果，以及此手術應用於二型糖尿病患者的臨床證據，並探討這技術在香港的可行性。

方法：通過PubMed和Elsevier論文搜索引擎進行系統性搜索。用以搜索文獻的關鍵詞為「胰腎聯合移植」(simultaneous pancreas and kidney transplantation)、「糖尿病」(diabetes)、「胰腺移植」(pancreas transplant)和「SPK」。原創和較重要的回顧文章均被納入研究範圍。所有囊括的文章均為1985年後以英文發表的論文。集中搜集關於移植後的臨床結果來比較不同的治療方法。按胰腎聯合移植和其他移植方法的臨床結果分為患者生存期、移植物存活期、糖尿病併發症和生活質量，並比較患者生存期和移植物存活期 。

結果：至目前為止臨床試驗的證據顯示胰腎聯合移植於一型糖尿病方面在患者生存期、移植物存活期、糖尿病併發症和生活質量均有良好結果。至於二型糖尿病方面，雖然手術效用和其具體應用仍存在爭議，但結果可能與一型糖尿病相若。

結論：胰腎聯合移植技術要求高，亦可能發生嚴重的併發症，因此應經過仔細篩選，例如當糖尿病併發症已危及病人生命或無法使用藥物和生理調節控制血糖水平的病人，才施以胰腎聯合移植作為「最後手段」。

SPK or LDKA achieves superior patient survival remains controversial. For short-term outcomes, the overall survival rate of SPK recipients has been shown

TABLE 1. Patient survival: summary of studies comparing different transplantation methods[4-19]

	Study, year of publication	No. of patients	Patient survival*
Short-term	Rayhill et al,[8] 2000	805	SPK = LDK > DDK
	Ojo et al,[9] 2001	9516	SPK = LDK > DDK
	Sutherland et al,[10] 2001	396	SPK = LDK = DDK
	Bunnapradist et al,[11] 2003	6016	SPK = DDK
	Reddy et al,[12] 2003	18 549	SPK = LDK > DDK
	Waki and Terasaki,[13] 2006	1088	SPK = DDK
	Young et al,[4] 2009	11 362	LDK > SPK = DDK
	Weiss et al,[14] 2009	8281	SPK+P > LDK > SPK-P = DDK
	Norman et al,[15] 2011	6282	SPK+P > SPK-P
	Sung et al,[19] 2015	11 253	SPK > KTA
Long-term	Becker et al,[16] 2000	642	SPK > LDK > DDK
	Mohan et al,[17] 2003	101	SPK > DDK
	Morath et al,[18] 2008	11 420	SPK > LDK > DDK
	Sollinger et al,[7] 2009	2100	SPK > LDK > DDK
	Morath et al,[5] 2010	15 118	SPK > LDK > DDK
	Lindahl et al,[6] 2013	630	SPK > LDK > DDK

Abbreviations: DDK = deceased donor kidney; KTA = kidney transplant alone; LDK = living donor kidney; SPK = simultaneous pancreas and kidney transplantation; SPK+P = functioning pancreas graft at 1 year after transplant; SPK-P = no functioning pancreas graft at 1 year after transplant
* '>' Denotes statistically significantly longer survival, and '=' no statistically significant difference in survival

to be almost equivalent to that of LDKA recipients, except in one large-scale study by Young et al[4] which yielded a better survival rate in LDKA patients after adjustment for high-risk characteristics in this group of patients. Consistent with other studies, the unadjusted overall patient survival was equivalent for SPK and LDKA. For long-term outcomes, SPK recipients had a higher survival rate than LDKA recipients. This may be because the additional beneficial effects of pancreas transplantation on glycaemic control need time to manifest. Morath et al[5] postulated that, over time, SPK would provide greater survival benefits since the initially higher associated operational mortalities would later be compensated by improved glycaemic control that reduced death from diabetic complications, particularly in terms of cardiovascular death. This view is further supported by the fact that the major cause of death in all these patients is primarily cardiovascular disease (62%), followed by infection (16%), malignancy (8%), and other causes (14%).[6] It also potentially explained why in Young et al's study,[4] despite initial superior patient survival following LDKA compared with SPK (1-year survival of LDKA, SPK, and DDKA was 97%, 95%, and 93%, respectively), the results began to favour SPK by the end of the 72-month study period.

Graft survival

The assessment of graft survival in SPK includes that of the kidney and the pancreas. For kidney graft survival, the review by Lindahl et al[3] found similar short-term (up to 10 years) kidney graft survival rates following SPK and LDKA; graft survival after DDKA was inferior. Long-term results (>10 years) showed that DDKA was inferior to both SPK and LDKA, and most long-term studies agreed that SPK was equivalent to LDKA, with the exception of a study by Morath et al[5] that showed SPK to be superior to LDKA. As such, the current view is that SPK is at least non-inferior to LDKA in terms of long-term kidney graft survival, even though most SPK in the literature reviewed were from cadaver donors (Table 2[4-6,8,10-20]).

For pancreas graft survival, the results from SPK have improved significantly over the past years due to improved surgical techniques and immunosuppressive regimens.[3] Surgical techniques have evolved from the use of pancreatic duct occlusion (1983-1987) to that of exocrine drainage into the urinary bladder (1988-1999), and later to that of direct drainage into the proximal jejunum (2000 onwards). With the latter, the mean pancreas graft survival rates after 1 and 5 years have been reported to be 87% and 75%, respectively.[3]

Diabetic complications

In the present context of transplantation therapy, the important complications of T1DM include diabetic nephropathy, diabetic neuropathy, and

TABLE 2. Kidney graft survival: summary of studies comparing different transplantation methods[4-6,8,10-20]

	Study, year of publication	No. of patients	Patient survival*
Short-term	Rayhill et al,[8] 2000	805	SPK = LDK > DDK
	Sutherland et al,[10] 2001	396	SPK = LDK = DDK
	Bunnapradist et al,[11] 2003	6016	SPK = DDK
	Reddy et al,[12] 2003	18 549	SPK = LDK > DDK
	Waki and Terasaki,[13] 2006	1088	SPK = DDK
	Young et al,[4] 2009	11 362	LDK > SPK = DDK
	Weiss et al,[14] 2009	8281	SPK+P > LDK > SPK-P = DDK
	Norman et al,[15] 2011	6282	SPK+P > SPK-P
	Sung et al,[19] 2015	11 253	SPK > KTA
Long-term	Becker et al,[16] 2000	642	SPK = LDK > DDK
	Mohan et al,[17] 2003	101	SPK = DDK
	Israni et al,[20] 2005	8323	SPK > DDK
	Morath et al,[18] 2008	11 420	SPK = LDK > DDK
	Morath et al,[5] 2010	15 118	SPK > LDK > DDK
	Lindahl et al,[6] 2013	630	SPK = LDK > DDK

Abbreviations: DDK = deceased donor kidney; KTA = kidney transplant alone; LDK = living donor kidney; SPK = simultaneous pancreas and kidney transplantation; SPK+P = functioning pancreas graft at 1 year after transplant; SPK-P = no functioning pancreas graft at 1 year after transplant
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an increased risk of cardiovascular diseases. For diabetic nephropathy, several studies have included kidney biopsy in graft assessment following SPK, so as to capture the early diabetes-related changes that might otherwise take time to manifest clinically. The common diabetes-related changes under electron microscopy include thickening of the glomerular basement membrane (GBM) and an increase in mesangial volume. The study by Bohman et al[21] was the first to perform kidney biopsy in two SPK patients and six KTA patients. Diabetes-related changes were seen in five of the six KTA recipients but not in any of the SPK recipients. Wilczek et al[22] included a larger sample size (20 SPK vs 30 KTA) with a mean postoperative biopsy time of 1 to 6.8 years. The associated changes under light and electron microscopy were significantly fewer in the SPK group than the KTA group. Bilous et al[23] biopsied 12 PAK patients before and at least 1.9 years after the pancreas transplant, and found no glomerular disease progression. They also compared the 12 PAK with 13 KTA patients, and found lower mesangial volume in the PAK group. Although most studies showed that the outcomes would be better in patients with SPK relative to those with KTA, whether the pancreas graft can halt nephropathy progression remains controversial. Nyberg et al[24] biopsied 11 SPK patients 2 to 4 years postoperatively, and found a mean increase in GBM thickness when compared with normal controls. While recurrence of diabetic nephropathy is still possible in the long run, current evidence nonetheless supports that SPK can at least delay the progression of diabetic nephropathy in comparison with KTA.

Apart from its effect on the kidney, a pancreas transplant in SPK may potentially improve other organ systems that can be affected by diabetes. Diabetic neuropathy is an example. Navarro et al[25] compared 115 pancreas recipients with 92 patients prescribed standard insulin therapy. Neurological status was assessed by clinical examination, nerve conduction studies, and autonomic function test. Results up to 10 years showed significant improvement in nerve conduction studies and slight improvement on clinical examination and autonomic index in the SPK group. We proposed that pancreas transplantation could potentially halt the progression of diabetic neuropathy and may even lead to a degree of neurological improvement.

Besides microvascular complications, macrovascular complications are a major concern in diabetic patients. Cardiovascular diseases, in particular coronary artery disease, contribute to a significant portion of mortality in T1DM patients. Whether SPK can provide benefit in this respect has been studied. Jukema et al[26] observed 32 SPK patients with 26 functioning pancreas grafts and six non-functioning pancreas grafts. Glycaemic control was measured by blood glucose level, and the progression of diffuse and focal coronary atherosclerosis was assessed by coronary angiography. It was found that in the presence of a functioning pancreas graft, glycaemic control was better and progression of coronary atherosclerosis was slower. This might also correlate with a lower risk of cardiovascular death and explain why long-term survival in SPK patients is superior to that of KTA patients.

Quality of life

In addition to survival benefit and reduced co-morbidity, improvement in QOL may also represent an important consideration. A functioning pancreas graft can potentially free a patient from the need for self-administered insulin and achieve more stable blood glucose levels.[27-29] These outcomes may be associated with improvement in QOL. To directly quantify such improvement, some studies have used validated health-related quality of life (HRQOL) questionnaires to evaluate treatment outcomes. The latest cohort study by Martins et al[30] compared the HRQOL scores of 126 patients before and after SPK with a follow-up duration of around 5 years. There were improvements in all domains under the Gastrointestinal Quality of Life Index post-transplantation, with a significant visual analogue scale health state improvement from 38% to 84%.[30] Assessment by another tool, the EuroQol-5 Dimension questionnaire, also showed improvement in physical function, psychological status, social function, gastro-intestinal complaints, burden of medical treatment as well as the rate of unemployment.[30] The majority of available studies have focused mainly on comparison of pre-transplant and post-transplant scores, or on transplanted and non-transplanted patients. Few studies have compared QOL outcomes between patients undergoing SPK and KTA. Sureshkumar et al[31] conducted a case-control study involving 27 SPK patients and 27 KTA patients. The authors concluded that SPK patients had a significantly better diabetes-related QOL.

Considerations in type 1 versus type 2 diabetes mellitus

Indications (in type 1 versus type 2 diabetes mellitus)

The predominant indication for SPK is T1DM patients with ESRD and adequate cardiac reserve who have no opportunity for a living donor kidney transplantation.[32] Currently, most centres will perform SPK mainly for T1DM, less commonly for T2DM patients. Nonetheless there has been pervasive controversy on whether the long-term outcomes of SPK in the two groups actually differ.

This has important implications in organ allocation as T2DM is much more prevalent than T1DM. Several factors have to be considered. First, there are differences in pathogenesis between the two conditions—T2DM is attributed to insulin resistance in addition to insulin secretion defect; in T1DM, the pathogenesis involves the auto-destruction of islet cells, causing absolute insulin deficiency. This would theoretically render pancreas transplantation less efficacious in T2DM. Second, there is as yet no consensus on the distinction between the two conditions. For example, C-peptide, which is used in patient selection for SPK between T1DM and T2DM patients, has been shown by some studies to be unreliable in determining the outcomes of SPK.[33] Third, it should be noted that there exists major differences between the two groups of diabetic patients that make meaningful comparison difficult. These include disproportionate sample sizes; the presence of confounders such as age, obesity, co-morbidities; and duration and treatment of the underlying diabetes.

Notwithstanding, there has been an increasing amount of evidence showing comparable results of SPK in selected T2DM and T1DM patients.[34] In a large study using the data obtained from the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) between 2000 and 2007, Sampaio et al[35] showed no significant difference in 5-year survival rate between T1DM and T2DM recipients despite the fact that the latter group had a higher risk of death due to older age and longer pre-transplant dialysis time. In the same study, the 5-year pancreas graft survival in T2DM patients (69.8%) was comparable with that in T1DM patients (72.4%); an inferior 5-year kidney graft survival was found (77.8% vs 73.5%; P=0.007).[35] After adjusting for other potential risk factors (eg time on dialysis, obesity), however, diabetes type was not identified as an independent prognostic factor.[35]

Concerning the role of C-peptide in defining T1DM and T2DM during patient selection, Stratta et al[36] stratified 162 SPK recipients according to pre-transplant C-peptide levels into C-peptide 'positive' (≥2.0 ng/mL; n=30) and C-peptide 'negative' (<2.0 ng/mL; n=132) groups. With a mean follow-up duration of 5.6 years, the two groups showed no statistically significant differences in pancreas graft, kidney graft, or patient survival.[36] In a similar study involving 80 SPK recipients, 10 were classified as T2DM and 70 as T1DM.[37] On Cox regression survival analyses, no statistically significant difference in graft and patient survival was found between the two groups.[37] The authors concluded that selected T2DM patients with ESRD should be considered potential candidates for SPK, and that the use of C-peptide as the predominant marker of the diabetes type was unreliable and potentially misleading.[37]

Simultaneous pancreas and kidney transplantation versus other transplant options in type 2 diabetes mellitus patients

At present, there is insufficient evidence to support the use of SPK over other kidney transplant options in patients with T2DM. In an early study that compared the outcomes of SPK, DDKA, and LDKA in patients with T2DM, Wiseman and Gralla[38] concluded that both patient and graft survival rates were superior with LDKA transplantation, whereas patient but not graft survival rate was higher in SPK versus DDKA transplantation. After multivariable analysis, the survival advantage of SPK over DDKA was related not so much to the pancreas transplantation but other variables such as younger donor and recipient ages in the SPK cohort (Table 3[38]). These findings, however, should not completely dismiss the consideration of SPK for selected T2DM patients who have little prospect for LDKA since other outcome measures such as the

TABLE 3. Comparison of outcomes between simultaneous pancreas and kidney transplantation and living/deceased donor kidney alone by Wiseman and Gralla[38]

	SPK	Kidney transplantation	P value
LDKA	(n=424)	(n=1987)	
Patient survival	82.0%	87.3%	0.003
Kidney survival	75.2%	81.2%	0.002
Death-censored kidney graft survival	86.2%	91.1%	0.003
DDKA	(n=424)	(n=4005)	
Patient survival	82.0%	75.5%	0.04
Kidney survival	75.2%	65.1%	0.004
Death-censored kidney graft survival	86.2%	82.6%	0.21

Abbreviations: DDKA = deceased donor kidney alone; LDKA = living donor kidney alone; SPK = simultaneous pancreas and kidney transplantation

benefits of euglycaemia in terms of better QOL and secondary complications of diabetes will also have to be considered. Nonetheless, given the superior long-term outcome of SPK over LDKA in T1DM patients and that the same has yet to be demonstrated in T2DM patients, T1DM patients should still be given a stronger allocation priority of SPK grafts.[3]

Complications of simultaneous pancreas and kidney transplantation

Most complications of SPK are related to the transplanted pancreas.[39] Repeated laparotomy may be required in up to 50% of patients.[40,41] The pancreatic graft survival at 1 year may range from 74% to 88%, with the sharpest drop during the first year.[7,39,42] The reported 10-year and 20-year survival rates were 63% and 36%, respectively.[7] Most complications occur within the first 60 days of operation and include graft pancreatitis (3%-12%), infection/abscess (1%-5%), focal/diffuse necrosis (12%), graft-vessel thrombosis (6%-17%), anastomotic leak (0.5%-2%), and intra-abdominal haemorrhage (0%-0.5%).[39-43] Venous thrombosis has been reported to be the most common cause of graft failure; graft pancreatitis and focal/diffuse necrosis were the most common causes of mortality among graft-specific complications.[39,40]

Complications related to the transplanted kidney include acute tubular necrosis (ATN) or graft rejection, urinary complications, infection, and vascular thrombosis. According to a study of 112 SPK recipients by Grochowiecki et al,[44] ATN and rejection were the most frequent (43.4%) causes leading to the loss of kidney graft function. Infections (28.6%) and vascular thrombosis due to atherosclerosis of the iliac arteries (28.6%) were the most common reasons for graft nephrectomy.[44] The most severe complications were due to fungal infection.[44] Overall, the 1-year survival rate for the kidney graft was over 90%.[7,44,45] The 10-year and 20-year kidney survival rates were 63% and 38%, respectively.[7] In terms of overall mortality, the most common causes following SPK have been reported to be cardiopulmonary (7.2%), followed by infection (3.4%), stroke (1.8%), and renal failure (1.5%). Patient survival rates at 1, 10, and 20 years were 97%, 80%, and 58%, respectively.[7]

Comparison of the complications of SPK versus KTA has revealed that SPK has a lower rate of ATN (8.9%)[44] than KTA (15.3%),[46] but a slightly higher rate of urological complications (4.5%)[44] than KTA (3.7%).[47] The incidence of vascular complications was comparable in SPK (1.8%)[44] and KTA (0.5%-4%).[48-50] As mentioned above, SPK has higher long-term patient and kidney survival rates than LDKA/DDKA.

Future directions and local applicability of simultaneous pancreas and kidney transplantation

Simultaneous pancreas and kidney transplantation has become an established treatment for patients with T1DM complicated by ESRD. The results have, so far, been promising. Furthermore, apart from SPK, newer techniques including pancreatic islet cell transplantation, and different combinations of living and/or deceased donor pancreas, islet cell and kidney graft transplantation are being evaluated. Current research aims to extend these techniques, still predominantly SPK, to the treatment of T2DM, for which LDKA remains the first-line treatment option. In situations where LDKA is not available for T2DM patients, DDKA remains the next best option. Regarding the ethical issues about graft allocation, the allocation of DDKA is based on an allocation system that takes account of patient age and waiting time as well as the degree of human leukocyte antigen (HLA) matching between the potential donor and the recipient.[51] Difficulties may arise, however, when a deceased donor with both kidney and a pancreas graft has become available. Should the priority for these grafts be given to a patient on the SPK waiting list or a non–diabetes-related ESRD patient on the DDKA waiting list? And should the priority of SPK be given to a T2DM patient who is higher up on the allocation system (with a younger age, a longer waiting time, or lesser degree of HLA mismatch) or to a T1DM patient who is lower on the allocation system but is more likely to achieve a better outcome? The related ethical issues clearly deserve an informed discourse within the surgical community.

Simultaneous pancreas and kidney transplantation has not yet been performed in this locality. The main obstacle remains the shortage of cadaver organs. Here, the number of cadaveric renal transplantations performed in the Hospital Authority over the last decade ranges from 44 to 87 cases per year. As of 31 December 2014, the number of patients waiting for transplantation was close to 2000. This translates into significantly prolonged dialysis time for this specific group of patients, and hence a potentially suboptimal outcome after SPK. The implementation of SPK would not be readily feasible unless there is a significant improvement in organ availability.

Conclusions

Simultaneous pancreas and kidney transplantation has become a standard treatment worldwide for patients with T1DM and ESRD. There is a large volume of clinical evidence supporting good

outcomes in patient survival, graft survival, diabetic complications, and QOL. For T2DM, the efficacy and application of the procedure remain controversial but the outcomes are possibly comparable to that in T1DM. Simultaneous pancreas and kidney transplantation is a technically demanding procedure that is associated with significant complications, and should be undertaken only in carefully selected patients. It should be regarded as a 'last resort' treatment for patients in whom diabetic complications have become life-threatening or severely burdensome despite best efforts in maintaining good diabetic control through lifestyle modification and medications. Continued efforts in patient education and the promotion of an altruistic culture of organ donation among the public are critical for the implementation of this treatment paradigm in this locality.

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