ORIGINAL ARTICLE

An analysis of the survival outcomes of simultaneous pancreas and kidney transplantation compared to live donor kidney transplantation in patients with type 1 diabetes: a UK Transplant Registry study

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SUMMARY

Transplant options for patients with type 1 diabetes and end-stage renal disease (ESRD) include deceased donor kidney, live donor kidney (LDK) and simultaneous pancreas-kidney (SPK) transplantation. The aim of this study was to compare outcomes between LDK and SPK for patients with type 1 diabetes and ESRD in the UK. Data on all SPK (n = 1739) and LDK (n = 385) transplants performed between January 2001 and December 2014 were obtained from the UK Transplant Registry. Unadjusted patient and kidney graft survival were calculated using the Kaplan–Meier method. Multivariate analysis of kidney graft and patient survival was performed using Cox proportional hazards regression. There was no significant difference in patient (P = 0.435) or kidney graft survival (P = 0.204) on univariate analysis. On multivariate analysis there was no association between LDK/SPK and patient survival [HR 0.71 (0.47–1.06), P = 0.095]. However, LDK was associated with an overall lower risk for kidney graft failure [HR 0.60 (0.38–0.94), P = 0.025]. SPK recipients with a functioning pancreas graft had significantly better kidney graft and patient survival than LDK recipients or those with a failed pancreas graft. SPK transplantation does not confer an overall survival advantage compared to LDK. However, those SPK recipients with a functioning pancreas have significantly better outcomes.

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Key words
kidney clinical, live donors, kidney clinical, pancreas clinical

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Introduction

Treatment options for patients with type 1 diabetes and end-stage renal disease (ESRD) range from dialysis through kidney transplantation alone, from either a live or a deceased donor, to kidney transplantation with beta-cell replacement, either in the form of a whole-organ pancreas or islet cell transplantation. There is good evidence that for suitable patients, kidney transplantation confers a significant survival advantage over remaining on dialysis [1]. What is less clear is which transplant option is the optimal treatment for patients with type 1 diabetes

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and end-stage renal disease. Analyses of large registry data from the Scientific Registry of Transplant Recipients (SRTR) in the United States [2] and the worldwide Collaborative Transplant Study [3] have demonstrated that deceased donor kidney transplantation is associated with significantly worse long-term patient and graft survival compared to simultaneous pancreas and kidney (SPK) transplantation. However, when comparing live donor kidney (LDK) with SPK transplantation, the evidence is contradictory. The Collaborative Transplant Study showed improved initial kidney graft survival after LDK transplantation, but worse long-term patient survival [3]; whereas analysis of the OPTN/UNOS database showed lower risk of kidney graft failure and patient death after LDK compared to SPK transplantation [4]. No such analysis has been performed in the United Kingdom and US data cannot necessarily be extrapolated to the UK given the marked differences in donor and recipient demographics. This relates mainly due to donor age and cause of death with a higher proportion dying due to a cerebrovascular accident in the UK. There is also a much smaller proportion of African American donors and recipients in the UK.

Greater clarity on the relative risks and benefits of these therapeutic options is essential to ensure patients and clinicians are fully informed and can make appropriate treatment choices. Therefore, the aim of this study was to compare the outcomes of live donor kidney transplantation and simultaneous pancreas and kidney transplantation using data from the UK Transplant Registry.

Patients and methods

Data on all simultaneous pancreas and kidney and live donor kidney transplants performed for type 1 diabetes between January 2001 and December 2014 were obtained from the UK Transplant Registry, prospectively maintained by NHS Blood and Transplant. Patients who had undergone solitary pancreas transplantation following live donor kidney transplantation were excluded from the analysis. Cases were closed for analysis on 7th December 2014; median follow-up was 3.3 years for the SPK group and 3.9 years for the LDK group.

As this study includes patients from all UK renal transplant centres, there was no standardized surgical technique with both bladder and enteric exocrine drainage used. The method of verifying type I diabetes also varied amongst centres with the majority utilizing C-peptide measurement, although some relied on clinical assessment including age of onset of diabetes. Pancreas graft failure was defined as return to exogenous insulin use, although some centres confirmed this with an absence of measureable C-peptide.

Donor, recipient and transplant characteristics were described using median [interquartile range (IQR)] following normality testing. The Wilcoxon rank-sum was used to test for differences in continuous variables and the chi-square test or Fisher's exact test for categorical variables. Unadjusted patient and graft survival were estimated using the Kaplan–Meier product limit method and compared using the log rank test. Kidney graft survival was determined from the date of transplant until the earlier of death, return to dialysis or retransplantation.

Multivariate estimates of hazards of kidney graft and patient survival were calculated using Cox proportional hazards regression. The proportional hazards assumption for the Cox model was met.

Statistical analysis was performed using GRAPHPAD PRISM (GraphPad, La Jolla, CA, USA) and SPSS (IBM, Armonk, NY, USA). All tests were two-tailed and differences considered significant when $P < 0.05$.

Results

Between January 2001 and December 2014, 1739 simultaneous pancreas and kidney and 385 live donor kidney transplants were performed in the UK for ESRD in patients with type 1 diabetes. Due to incomplete survival data fifteen live donor kidney transplants were excluded, leaving 1739 SPK and 370 LDK transplants for analysis.

Baseline donor, recipient and transplant characteristics are shown in Table 1. As expected, live kidney donors were significantly older than SPK donors, had a significantly higher BMI and were more likely to be female. Intracranial haemorrhage or thrombosis accounted for 58% of deaths in SPK donors and the majority (88%) were donation after brain stem death (DBD) donors. Similarly, live donor kidney recipients were significantly older and had a significantly higher BMI. In addition, they were more likely than SPK recipients to be on haemodialysis prior to transplantation. Donor–recipient HLA mismatch was significantly greater in SPK transplants, but there were significantly more repeat kidney transplants in LDK patients. There was no difference in waiting time for transplant between the two groups.

Delayed graft function was significantly more likely following SPK compared to LDK transplantation

Table 1. Donor, recipient and transplant characteristics of live donor kidney and simultaneous pancreas kidney study groups.

	SPK (n = 1739)	LDK (n = 370)	P value
Donor characteristics			
Age (years)	36 (23–46)	48 (40–57)	<0.0001
Sex (M:F)	854:885 (49%:51%)	149:221 (40%:60%)	0.0028
Body mass index	23.6 (21.5–26.0)	27 (24.2–29.4)	<0.0001
Cause of death			
Intracranial haemorrhage/thrombosis	1010 (58%)		
Trauma	291 (17%)		
Hypoxic brain injury	247 (14%)		
Meningitis	44 (3%)		
Brain tumour	25 (1.5%)		
Suicide	11 (0.5%)		
Cardiac	10 (0.5%)		
Other	84 (5%)		
Unknown	5 (0.25%)		
Recipient characteristics			
Age (years)	41 (36–48)	47 (39–54)	<0.0001
Sex (M:F)	1025:714 (59%:41%)	204:166 (55%:45%)	0.2164
Body mass index	24.4 (22.0–27.3)	26.1 (23.1–29.3)	<0.0001
Waiting time for transplant (days)	316 (117.3–596)	329 (111–679)	0.5471
Dialysis modality			
Haemodialysis	545 (31%)	154 (42%)	0.0004
Peritoneal dialysis	432 (25%)	65 (18%)	
Predialysis	688 (40%)	130 (35%)	
Unknown	74 (4%)	18 (5%)	
Ethnicity			
White	1576 (90%)	333 (90%)	0.6112
Asian	90 (5%)	26 (7%)	
Black	51 (3%)	9 (2%)	
Other	16 (1%)	2 (1%)	
Unknown	6 (1%)	0	
Transplant characteristics			
HLA mismatch			
0	12 (1%)	37 (1%)	<0.0001
(0 DR and 0/1 B)	116 (7%)	55 (15%)	
(0 DR and 2B) or (1 DR and 0/1 B)	541 (31%)	166 (44%)	
(1 DR and 2 B) or (2 DR)	1070 (61%)	112 (30%)	
Transplant number			
1st	1668 (96%)	325 (88%)	<0.0001
2nd	62 (3%)	43 (11.5%)	
3rd or more	9 (1%)	2 (0.5%)	
Donor type			
Donation after brain death	1530 (88%)		
Donation after circulatory death	209 (12%)		
Cold ischaemic time (mins)	720 (600–857)	171 (92–232)	

LDK, live donor kidney; SPK, simultaneous pancreas-kidney.

Continuous data presented as median (interquartile range).

[15.5% vs. 7.3%, OR 2.24 (95% CI 1.46–3.44), $P < 0.0001$], although there was no difference in primary nonfunction rates between SPK and LDK groups [1.4% vs. 0.8%, OR 1.66 (95% CI 0.50–5.56, $P = 0.604$]. There was also no difference in kidney graft rejection rates within the first year post-transplant [SPK 11.6% vs. LDK 11.4%, OR 1.02 (95% CI 0.68–1.53), $P = 1.000$]. Furthermore, there was no difference in overall serum creatinine levels at 3 months, 1, 5 and 10 years post-transplant ($P = 0.685$). Primary nonfunction

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of pancreas grafts in the SPK group was 1.5%, and pancreas rejection rate within the first year post-transplant was 12.2%.

Kidney graft survival in LDK recipients was 99%, 92% and 77% compared to 96%, 89% and 80% in SPK recipients at 1, 5 and 10 years, respectively. Pancreas graft survival in the SPK recipients was 86%, 76% and 68% at 1, 5 and 10 years, respectively. A comparison of SPK patients who received grafts from DBD or donation after circulatory death (DCD) donors showed no differences in pancreas graft ($P = 0.329$), kidney graft ($P = 0.519$) or patient survival ($P = 0.142$).

Unadjusted death-censored kidney graft survival was not different between LDK or SPK recipients [HR = 1.23 (95% CI 0.86–1.76), $P = 0.252$] (Fig. 1). Similarly, there was no difference in unadjusted patient survival from the time of transplant between the two groups [HR = 0.87 (95% CI 0.63–1.21), $P = 0.417$] (Fig. 2). There was no difference in these findings when analysis was confined only to patients undergoing their first transplant, or when analysed by different transplant eras (2001–2007 vs. 2008–2014).

Multivariate Cox regression analysis revealed that older donor age [HR = 1.02 (95% CI 1.01–1.04), $P < 0.0005$] and female recipient [HR = 1.34 (95% CI 1.02–1.79), $P = 0.034$] were independently associated with worse kidney graft survival; whilst older recipient age [HR = 0.98 (95% CI 0.96–0.99), $P = 0.003$] and LDK transplantation [HR = 0.60 (95% CI 0.38–0.94), $P = 0.025$] were independently associated with improved kidney graft survival (see Table 2). On similar analysis, factors associated with worse recipient survival were increased donor age [HR = 1.01 (95% CI 1.00–1.03), $P = 0.02$) and increased recipient age [HR = 1.05 (95% CI 1.03–1.09), $P < 0.0005$], whereas predialysis status at registration for transplant [HR = 0.67 (95% CI 0.49–0.93), $P = 0.017$] was independently associated with improved recipient survival (see Table 3). Transplant type (LDK versus SPK) had no independent effect on patient survival [HR = 0.71 (95% CI (0.47–1.06), $P = 0.095$].

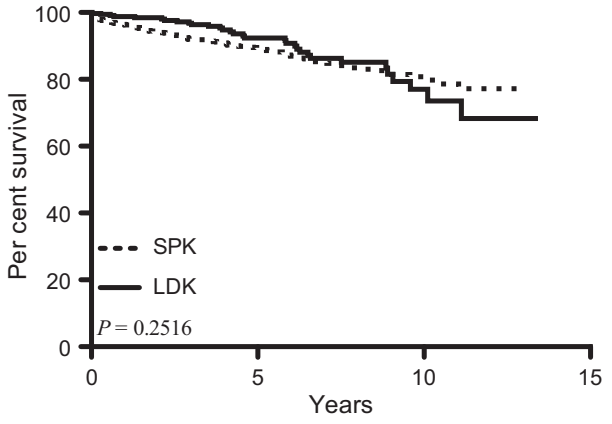

Figure 1 Kaplan–Meier curve of death censored kidney graft survival from time of transplant.

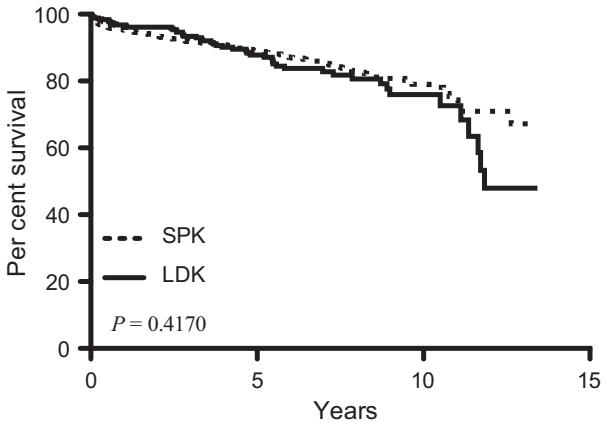

Figure 2 Kaplan–Meier curve of unadjusted patient survival from time of transplant.

There was no difference in the cause of kidney graft loss following LDK or SPK transplantation, and death with a functioning graft was the commonest cause in both groups, followed by rejection (see Table 4). Death with a functioning graft accounted for 37% of all kidney graft losses in the SPK group and 52% in the LDK group; this represented 6.7% of all SPK recipients and 10% of all LDK recipients. Cause of death was also similar between the two groups of patients; cardiac causes being the single commonest reason, with similar rates in LDK and SPK recipients (19% of deaths vs. 17% respectively, $P = 0.439$) (see Table 5). Notably, 8% of deaths in the SPK group were due to peri- or postoperative haemorrhagic complications with no such events in the LDK patients.

To evaluate the impact of pancreas graft survival on recipient and kidney graft survival, separate analysis was performed in SPK recipients with or without a functioning pancreas graft compared to the LDK group. SPK recipients with a functioning pancreas graft had significantly better kidney graft and patient survival than those with an LDK transplant, who in turn had a better kidney graft and patient survival than SPK recipients with a failed pancreas transplant (all $P < 0.001$). In this analysis, time of pancreas loss is a potential confounder, as late pancreas loss can be due to chronic rejection which may also affect the kidney. To adjust for this and examine the influence of only early graft

Table 2. Cox proportional hazards regression of kidney graft survival.

Covariate	Reference	Adjusted hazard ratio (95% CI)	*P* value
Donor			
Age		1.02 (1.01–1.04)	<0.0005
Sex		0.92 (0.69–1.22)	0.562
BMI		1.02 (0.98–1.06)	0.290
Ethnicity			0.455
Recipient			
Age		0.98 (0.96–0.99)	0.003
Female	Male	1.4 (1.02–1.79)	0.034
Dialysis			0.311
Ethnicity			0.460
Transplant			
Transplant number		0.88 (0.45–1.72)	0.702
HLA mismatch			0.699
LDK	SPK	0.60 (0.38–0.94)	0.025

LDK, live donor kidney; SPK, simultaneous pancreas-kidney.

Table 3. Cox proportional hazards regression of patient survival from the time of transplant.

Covariate	Reference	Adjusted hazard ratio (95% CI)	*P* value
Donor			
Age		1.01 (1.00–1.03)	0.020
Sex		0.81 (0.61–1.07)	0.137
BMI		1.00 (0.96–1.04)	0.890
Ethnicity			0.983
Recipient			
Age		1.05 (1.03–1.09)	<0.0005
Sex		1.08 (0.82–1.43)	0.582
Peritoneal dialysis*	Haemodialysis*	0.93 (0.67–1.31)	0.689
Predialysis*	Haemodialysis*	0.67 (0.49–0.93)	0.017
Ethnicity			0.630
Transplant			
Transplant number		1.49 (0.92–2.41)	0.108
HLA mismatch			0.622
LDK	SPK	0.71 (0.47–1.06)	0.095

LDK, live donor kidney; SPK, simultaneous pancreas-kidney.

*Dialysis modality at time of transplant.

Table 4. Cause of kidney graft loss.

Cause of failure	SPK, *n* = 315 (%)	LDK, *n* = 71 (%)
Rejection	76 (24)	11 (15)
Recurrent nephropathy	3 (1)	2 (3)
Vascular or ureteric (excluding thrombosis)	10 (3)	1 (1)
Vascular thrombosis	10 (3)	1 (1)
Infection of graft	4 (1)	1 (1)
Removal of functioning graft	0	1 (1)
Nonviable kidney	6 (2)	2 (3)
Death with a functioning graft	117 (37)	37 (52)
Other	61 (19)	9 (13)
Unknown	27 (9)	6 (8)

LDK, live donor kidney; SPK, simultaneous pancreas-kidney.

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Table 5. Causes of death in patients following transplantation.

	SPK, n = 201 (%)	LDK, n = 51 (%)
Cardiac	34 (17)	10 (19)
CVA	6 (3)	2 (4)
Postop haemorrhage	16 (8)	0
Other	31 (15)	11 (21)
Pneumonia	10 (5)	5 (10)
Septicaemia	14 (7)	4 (8)
Malignancy	10 (5)	3 (6)
Respiratory failure	7 (3)	1 (2)
Multi-organ failure	6 (3)	0
Unknown	67 (33)	15 (29)

LDK, live donor kidney; SPK, simultaneous pancreas-kidney.

loss, effects of early pancreas loss within 90 days of transplantation on kidney graft and patient survival were analysed, conditioned on 90 days survival. This showed that SPK recipients who had a functioning pancreas for at least 90 days had significantly better patient survival than both LDK recipients ($P = 0.0442$) and SPK recipients whose pancreas failed within the first 90 days ($P = 0.0002$) (Fig. 3). When kidney graft survival was analysed conditional on 90 days pancreas survival, there was no difference between SPK recipients who had a functioning pancreas for at least 90 days and LDK recipients ($P = 0.2503$), or SPK recipients whose pancreas failed within 90 days ($P = 0.0507$) (Fig. 4).

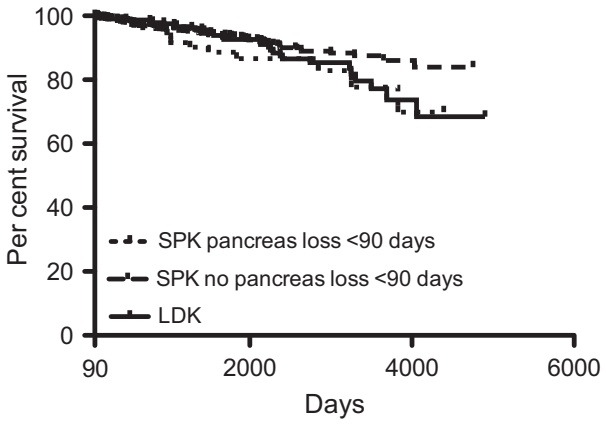

Figure 3 Kaplan–Meier curve of unadjusted kidney graft survival from time of transplant including patients with loss of pancreas graft within 90 days from transplant, no loss of pancreas graft within 90 days from transplant and live donor kidney graft. Analysis conditional on 90 days pancreas survival.

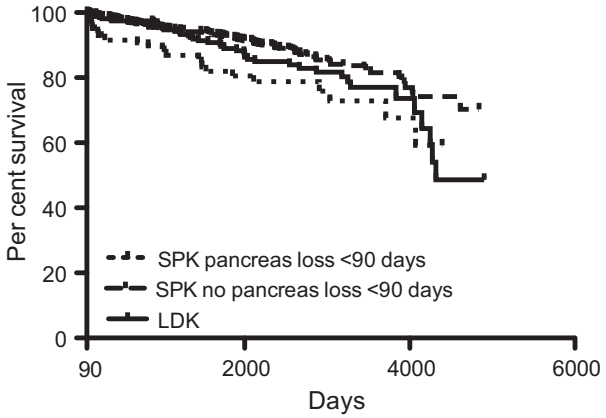

Figure 4 Kaplan–Meier curve of unadjusted patient survival from time of transplant including patients with loss of pancreas graft within 90 days from transplant, no loss of pancreas graft within 90 days from transplant and live donor kidney graft. Analysis conditional on 90 days pancreas survival.

Discussion

This study compared outcomes of live donor kidney transplantation with simultaneous pancreas and kidney transplantation for patients with ESRD and type 1 diabetes in the United Kingdom. It demonstrates no overall difference in patient survival between the two groups, although importantly those SPK recipients with a functioning pancreas graft at 90 days had significantly better patient survival and similar kidney graft survival to LDK recipients. Nevertheless, LDK transplantation was found to be an independent predictor of improved kidney graft survival compared to SPK transplantation.

Similar studies of large transplant registries have reported differing findings, potentially due to variable lengths of follow-up or differences in donor and recipient demographics. Interrogation of the OPTN/UNOS database found on multivariate analysis that LDK transplantation was associated with significantly lower risks of kidney graft failure and patient death [4]. However, the follow-up period was only 72 months and this may introduce bias against SPK transplantation, which has a higher early mortality than LDK transplantation. Consistent with this, a prior study of the UNOS database with longer follow-up demonstrated equivalent patient survival in SPK and LDK recipients [5], as did a similar study of the US SRTR [6]. Conversely data from the Collaborative Transplant Study demonstrated significantly better survival for SPK recipients compared with LDK recipients from years 10 to 20 following transplant [3]. However, there was no difference in kidney graft survival between the two groups. Therefore, there appears to be time-dependent differences in the relative survival advantage of SPK and LDK transplantation. Of note, in the current study, there was no difference in

patient survival at any time point following transplant although the number of patients at risk in both groups beyond 10 years of follow-up was small. However, arguably what is important to the patient when making decisions about treatment options is overall survival post-transplantation and this should therefore be the outcome such comparisons focus on.

The outcome measures used in this study are limited by the data collected by the UK Transplant Registry. As such, there is no comparison of progression of diabetic complications, diabetic control, hypoglycaemic unawareness or quality of life between the two transplant modalities. While previous studies have investigated the influence of SPK transplantation on diabetic complications including neuropathy [7], retinopathy [8] and nephropathy [9] the majority are insufficiently controlled or powered to be conclusive. Very few studies have compared progression of diabetic complications following SPK and LDK transplantation, despite the importance of controlling for the effect of kidney transplantation alone, as some improvements may be due to restoration of normal renal function. Nevertheless, one study has compared long-term cardiovascular mortality following SPK and LDK transplantation, adjusting for cardiovascular comorbidity, and demonstrated a significant reduction in SPK recipients [10]. In contrast, the current study did not show any difference in cardiovascular mortality between the two transplant modalities.

There are inherent limitations of a retrospective analysis of prospectively maintained registry data such as this. No data were available on pretransplant severity of diabetes, cardiovascular morbidity or diabetic complications to allow risk adjustment between the groups. Despite adjustment using multivariate models, there may be unaccounted risk factors present that affect the outcomes. There may also be centre-specific bias, as only one-third of UK kidney transplant centres also perform pancreas transplantation. Nevertheless, submission of data to the UK Transplant Registry is mandatory and survival data was complete. Incomplete reporting, therefore should not affect analysis of transplant outcomes. However, there were significant missing data for other fields that precluded their inclusion in the multivariate modelling; these were recipient BMI, recipient smoking history and time from placement on the transplant waiting list.

It is of note that the proportion of pre-emptive transplants was similar for live donor kidney and simultaneous pancreas kidney transplant. This does not appear to reflect an under utilisation of pre-emptive live donor kidney transplantation as the UK rates reported here compare well with those from the United States [11] and are better than the Eurotransplant rates. Therefore, the similarity in pre-emptive rates amongst SPK and LDK appears to reflect a higher usage of pre-emptive SPK in the UK compared to other countries. Similarly, it is also surprising that LDK transplantation is not associated with shorter waiting times than SPK transplantation. However, there are a number of LDK recipients who were never placed on the deceased donor waiting list, and as such are not included in the statistics for waiting times.

The aim of this study was to provide evidence to inform discussions and decision-making by clinicians and patients who have the options of either a live donor kidney or simultaneous pancreas and kidney transplant. On the basis of this study, SPK cannot be considered to provide an overall patient survival advantage and kidney survival appears to be inferior, and patients should be counselled accordingly. Factors other than patient and graft survival should also be considered when choosing transplant options. The presence of brittle diabetes and hypoglycaemic unawareness, for example, may prompt a preference for SPK transplantation to treat these complications. Patient preference and choice is also critical, as patients whose diabetes and its management have a profound effect on their quality of life may derive greater benefit from SPK transplantation. Conversely, patients in whom renal failure and its management, particularly dialysis, is more detrimental may benefit more from live donor kidney transplantation, the waiting time for which is likely to be significantly shorter than for SPK transplantation. Comorbidities and fitness for surgery should also be taken into account, and patients deemed high risk for SPK transplantation are likely to benefit more from a live donor kidney transplant.

A key finding of this study, supported by other studies [12,13], is the importance of pancreas graft function in determining long-term outcomes of SPK transplantation. The primary reason for the lack of overall benefit of SPK appears to be the detrimental effects of pancreas graft loss on patient survival. This is not surprising as loss of the pancreas essentially leaves SPK recipients with a deceased donor kidney, outcomes of which are known to be inferior to both SPK and LDK transplantation for diabetic recipients. Given this, the focus of clinicians should therefore be on maximising pancreas graft outcomes. This should include efforts to improve donor selection, pancreas assessment, organ preservation [14], reduction of cold ischaemia and management of complications. Centre outcomes for pancreas transplantation

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should also be methodically and regularly audited, as occurs in the UK, to ensure quality improvement. Given the above, patients may also consider selecting centres with better reported outcomes, in an attempt to maximise their survival benefit from an SPK transplant.

Patients who undergo live donor kidney transplantation are not precluded from undergoing pancreas transplantation at a later date. However, the proportion of patients undergoing pancreas after live donor kidney transplantation is small, comprising only 7% of patients on the waiting list for a kidney and/or pancreas transplant in the United States [11] and accounts for only 1.5% of transplants in the UK for type 1 diabetes. This is partly due to concerns about worse pancreas graft outcomes compared to SPK transplantation [11,15], as well as the potential detrimental impact of the additional immunosuppression required at the time of pancreas transplantation on the function of the previous kidney graft. However, a strategy of live donor kidney transplantation followed by pancreas transplantation has been shown in the United States to be associated with better kidney graft function, shorter dialysis time and more pre-emptive transplantation compared to SPK transplantation [11]. A further egalitarian advantage of promoting live donor kidney transplantation in this setting is that it adds another kidney graft to the overall pool, which we know is smaller than the number of patients on the waiting list.

In conclusion, based on this UK data, simultaneous pancreas and kidney transplantation does not confer an overall patient survival advantage over live donor kidney transplantation for end-stage renal disease due to type 1 diabetes. Indeed, kidney graft survival is superior following live donor kidney transplant. However, those SPK recipients with a functioning pancreas at 90 days had better long-term patient survival and comparable kidney graft survival to LDK recipients. Therefore, decisions about treatment options in these patients should not necessarily be focused on patient survival, but also be based on other factors such as hypoglycaemic unawareness, fitness for surgery and patient priorities. For those choosing combined kidney and pancreas transplantation every effort should be given to securing long-term pancreas function to allow patients to benefit from the improved survival this brings.

Authorship

All authors conceived the study, analysed data and drafted the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

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