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ARTICLE

# Simultaneous islet–kidney vs pancreas–kidney transplantation in type 1 diabetes mellitus: a 5 year single centre follow-up

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**Abstract**
*Aims/hypothesis* The aim of this study was to compare the long-term outcomes—in terms of glucose control, renal function and procedure-related complications—of simultaneous islet–kidney (SIK) transplantation with those of simultaneous pancreas–kidney (SPK) transplantation in patients with type 1 diabetes mellitus.
*Methods* $HbA_{1c}$, need for insulin, GFR and complication rate were compared between 13 recipients of SIK and 25 recipients of SPK transplants at the same institution. The mean follow-up was 41 months.
*Results* Two primary organ non-functions occurred in the SIK group. $HbA_{1c}$ did not differ at any time point during follow-up in the SIK group compared with the SPK group (mean during follow-up 6.3 vs 5.9%). Similarly, kidney function over time was not different between the two groups. A higher rate of insulin independence following SPK transplantation (after 1 year 96 vs 31% in the SIK group) was counterbalanced by a higher rate of serious adverse events (40% relaparotomies vs 0% in the SIK group).
*Conclusions/interpretation* The endogenous insulin production achieved by islet transplantation, combined with optimal insulin therapy, was sufficient for maintaining near-normal glucose levels. In terms of glucose control, islet transplantation provides results comparable to those achieved with pancreas transplantation. However, SPK results in a higher rate of insulin independence, albeit at the cost of more surgical complications. These results have led to a new paradigm in islet transplantation at our institution, where the primary goal is not insulin independence, but good glucose control and avoidance of severe hypoglycaemia.

**Keywords** CGMS (continuous glucose monitoring system) · GFR (glomerular filtration rate) · Hypoglycaemia · Insulin independence · Islet transplantation · Kidney transplantation · Pancreas transplantation · Surgical complications · Type 1 diabetes mellitus

**Abbreviations**

| | |
|---|---|
| CGMS | continuous glucose monitoring system |
| IEQ | islet equivalents |
| KTA | kidney transplantation alone |
| MDRD | modification of diet in renal disease |
| SIK | simultaneous islet–kidney transplantation |
| SPK | simultaneous pancreas–kidney transplantation |

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## Introduction

Transplantation of isolated islets of Langerhans is an accepted treatment option for patients with type 1 diabetes mellitus. In 2000, insulin independence was achieved consistently with a steroid-free immunosuppression protocol [1]. Islet transplantation, therefore, has emerged as an alternative to whole-organ pancreas transplantation, a procedure which has been carried out since 1966 [2], mainly as simultaneous pancreas–kidney transplantation (SPK) in patients with type 1 diabetes mellitus and renal failure due to diabetic nephropathy.

At the University Hospital of Zurich, a tertiary referral hospital, SPK transplantation has been performed since 1973. In 2000, the procedure and immunosuppression protocol were standardised according to results published by Sollinger et al. [3]. In the same year, the clinical islet transplant programme was initiated using the Edmonton protocol [4]. Both treatment options have been offered to patients with type 1 diabetes mellitus and end-stage renal failure. Transplantation of pancreatic beta cells, either as transplantation of the whole pancreas or of isolated islets, is performed at our institution exclusively in combination with kidney transplantation. SPK is an intervention with proven benefits in terms of survival [5], whereas in pancreas transplantation alone controversial results have been published [6, 7].

To the best of our knowledge, no data exist that directly compare the long-term outcome of these two combined transplantation modalities. The outcome in a heterogeneous group of patients receiving whole-organ pancreas transplantation (with or without transplantation of a kidney) was compared with islet transplantation alone during a mean follow-up of 15 months [8], with the authors reporting islet transplantation alone to be safer than whole-organ transplantation, but with a shorter duration of insulin independence. However, little is known about differences in long-term outcome between simultaneous islet–kidney (SIK) and SPK transplantation.

A randomised design for direct comparison is not ethically justifiable due to the overt differences with regard to the surgical procedures. For this reason, we considered a retrospective analysis of patients who had received either SIK or SPK to be a valuable alternative for quantification and comparison of different outcome parameters.

The aim of this study was to compare SIK and SPK with regard to differences in demographic characteristics and outcome parameters such as $HbA_{1c}$, need for exogenous insulin, renal function and complications.

## Methods

*Study design* Patients who underwent SPK or SIK at the University Hospital of Zurich between 1 January 2000 and 31 December 2004 were included. Study entry was defined as date of transplantation. Follow-up ended on 31 December 2005 or earlier if either of the following occurred: death of a patient or retransplantation of the kidney.

*Patient selection* Eligibility criteria were: type 1 diabetes mellitus and end-stage renal failure with need for dialysis treatment. Patient selection for one of the protocols was performed after careful evaluation of possible advantages and disadvantages, with special regard to age and comorbidities. Patients considered to be at higher risk of intraoperative complications were preferentially assigned to the less invasive procedure of islet transplantation, while younger and healthier patients were offered both modalities. To separate the effect of either of the two interventions from the effect of other transplantation-associated effects, we included a group of patients with type 1 diabetes who received kidney transplantation alone (KTA). As KTA is rarely performed in patients with type 1 diabetes mellitus at our institution, all KTA recipients with type 1 diabetes between 1996 and 2004 were included.

*Organ procurement and surgical procedures* Kidneys and pancreata were obtained from brain-dead multi-organ cadaver donors from different hospitals in Switzerland. Written informed consent was given by the closest relatives. A negative serum cross-match between donor and recipient and AB0 compatibility was required. Organs of donors were preferentially allocated to recipients of a comparable age.

The transplantation of the pancreas was performed heterotopically into the abdomen. Portal drainage was applied through venous anastomosis between the pancreas and the patient's superior mesenteric vein. The arterial access of the transplant was connected to the common iliac artery. All patients received an exocrine enteric drainage.

Preparation and transplantation of the pancreatic islets were performed as previously described [4]. Transplanted islets were not cultured before transplantation. Islet volume is given as islet equivalents (IEQ) [9].

The islet transplantation protocol was submitted to the ethics committee of the University Hospital Zurich and written informed consent was obtained from each patient.

The kidney transplantation was performed in the same way in all patients by heterotopical transplantation of the graft into the right or left iliac fossa and connection of the renal vein and artery to the iliac vessels.

*Immunosuppression* In the SPK group, a regimen with tacrolimus (Astellas Pharma, Villars-sur-Glâne, Switzerland) [10] and mycophenolate mofetil (Roche Pharma, Basel, Switzerland) [11], as well as prednisone (Streuli Pharma, Uznach, Switzerland) was used. Induction therapy was performed with basiliximab (Novartis Pharma, Basel, Switzer-

land). Target long-term trough levels for tacrolimus were 8 to 10 μg/l. Mycophenolate mofetil was administered twice daily in doses of 1 g. Immunosuppression in patients receiving KTA did not differ from that in SPK recipients with the exception that there was no induction therapy.

In the SIK group, immunosuppression was carried out with tacrolimus and sirolimus (Wyeth Pharma, Zug, Switzerland), according to the Edmonton protocol [1]. Induction therapy was performed with daclizumab (Roche Pharma, Basel, Switzerland). Target long-term trough levels were 7 to 10 μg/l for sirolimus and 3 to 6 μg/l for tacrolimus.

*Follow-up* During follow-up, pancreas or islet transplant function was assessed by $HbA_{1c}$ measurement (reference values in healthy adults 4.8–5.9%) and need for insulin. In SIK recipients, C-peptide secretion was measured during a mixed-meal tolerance test [4] at least every year after transplantation. Because of the high rate of insulin independence, C-peptide was not routinely measured after SPK. However, we did assess islet function by C-peptide and insulin stimulation during a mixed-meal test in a representative sample of five patients. In addition, current continuous glucose monitoring system (CGMS) measurements were performed in two representative subgroups from the SIK ($n$=5) and SPK ($n$=5) groups for the assessment of blood glucose control. Renal function was assessed by serum creatinine and GFR estimated by the four-parameter modification of diet in renal disease (MDRD) formula [12]. For follow-up analysis of organ function, organs with primary non-function, defined as continued need for dialysis or absence of stimulated C-peptide (C-peptide <0.2 nmol/l [13]) after transplantation, were excluded. All patients were seen at least every 6 months for evaluation of transplant function and adverse events. For assessment of cardiovascular risk, blood pressure, triacylglycerols, total cholesterol and both HDL-and LDL-cholesterol were measured, in addition to glycaemic control. All patients were treated according to current international guidelines. In particular, insulin treatment after transplantation, if necessary, was carried out with the same regimen and intensity as before transplantation.

*Cost analysis* A full-cost analysis of pancreas and islet transplantation was performed between April 2002 and February 2003 to evaluate the economic impact of the choice of either of the two treatment options. The cost analysis included the following: technical costs, nursing care, interdisciplinary medical care, medications, and length of hospital stay (not including pre-transplantation workup, follow-up, and rehospitalisations due to complications).

*Statistical analysis* Data are described as means±SD or relative frequencies. For the analysis of categorical frequency data, the $\chi^2$ and Fisher's exact probability procedures were applied. For comparison of continuous variables in two independent groups, $t$ test and Mann–Whitney test were used. A value of $p<0.05$ was considered significant. The Bonferroni correction was performed to account for multiple comparisons ($p<0.01$ was considered significant in a 5 year follow-up). (Multiple) linear regression was used for the testing of correlations.

## Results

*Patient characteristics* Altogether 38 patients were included in the study, 25 of whom received SPK and 13 SIK transplants. The demographic characteristics of the patients are shown in Table 1.

Sex distribution was equal in both groups. The age of the patients differed significantly ($p$=0.0001) between the two groups, as did the duration of diabetes ($p$=0.0009) before transplantation. SIK patients also had a slightly higher BMI ($p$=0.03). One of the most important comorbidities influ-

**Table 1** Patient demographics of patients with SPK, SIK or KTA transplantation

| Characteristic | SPK | SIK | $p$ value (SPK vs SIK) | KTA | $p$ value (KTA vs SPK/SIK) |
|---|---|---|---|---|---|
| $n$ | 25 | 13 | – | 11 | – |
| Sex, male/female (%) | 52/48 | 46/54 | 1.00 | 45/55 | 1.00 |
| BMI (kg/m$^2$) | 22.4±2.1 | 24.7±3.1 | 0.03 | 21.9±4.8 | 0.60 |
| Age at diagnosis of type 1 diabetes (years) | 9.6±3.7 | 10.9±10.6 | 0.61 | 17.9±7.6 | 0.003 |
| Age at transplantation (years) | 39.9±6.0 | 52.6±9.5 | 0.0001 | 49.5±7.6 | 0.04 |
| Diabetes duration (years) | 30.3±7.1 | 41.7±9.1 | 0.0009 | 31.6±8.4 | 0.53 |
| CHD % | 40 | 62 | 0.30 | 18 | 0.16 |
| Intervention for CHD % | 12 | 46 | 0.04 | 18 | 1.00 |
| Pretransplant dialysis (months) | 19.4±14.0 | 28.5±22.5 | 0.29 | 42.8±29.1 | 0.03 |
| Time on waiting list (months) | 12.8±11.5 | 16.6±16.7 | 0.49 | 21.5±14.4 | 0.07 |

Values are means±SD or percentages

**Table 2** Donor characteristics of the SIK group

| Patient number | Tx (*n*) | Donor age (years) | Donor weight (kg) | Cold ischaemia time (h:min) | Total IEQ per Tx | Total islet number per Tx | Isolation index (Islet equivalents/number of islets) |
|---|---|---|---|---|---|---|---|
| SIK 1 | 5 | 51.2±9.1 | 72.6±9.9 | 5:59±2:14 | 359,473±117,487 | 227,300±91,698 | 1.69±0.54 |
| SIK 2 | 4 | 51.0±17.4 | 100.0±47.3 | 5:48±3:27 | 317,510±101,640 | 258,750±204,873 | 1.64±0.78 |
| SIK 3 | 3 | 50.6±12.5 | 74.7±15.5 | 5:30±1:13 | 372,204±144,496 | 218,333±15,373 | 1.70±0.66 |
| SIK 4 | 1 | 35.7 | 100.0 | 4:46 | 324,644 | 194,000 | 1.67 |
| SIK 5 | 3 | 41.0±3.4 | 86.7±12.6 | 7:11±1:56 | 414,532±210,351 | 237,667±135,463 | 2.22±1.78 |
| SIK 6 | 2 | 47.4±14.7 | 81.9±8.6 | 5:36±1:25 | 374,772±193,150 | 201,500±130,815 | 1.96±0.32 |
| SIK 7 | 1 | 42.1 | 71.0 | 2:44 | 279,703 | 214,000 | 1.31 |
| SIK 8 | 4 | 56.0±12.7 | 84.5±11.4 | 6:51±1:57 | 402,469±207,688 | 184,250±32,806 | 2.14±1.01 |
| SIK 9 | 1 | 53.3 | 57.0 | 7:23 | 135,992 | 245,000 | 0.56 |
| SIK 10 | 1 | 62.1 | 75.0 | 9:12 | 335,336 | 232,000 | 1.45 |
| SIK 11 | 1 | 51.0 | 78.0 | 2:54 | 375,389 | 145,000 | 2.59 |
| SIK 12 | 1 | 56.8 | 70.0 | 7:08 | 270,314 | 366,500 | 0.74 |
| SIK 13 | 1 | 60.3 | 77.0 | 12:00 | 153,564 | 342,000 | 0.45 |
| Mean | 2.2±1.3 | 50.5±11.0 | 81.3±20.08 | 6:19±2:26 | 345,070±137,511 | 229,214±100,214 | 1.71±0.86 |

Values given as ± are means±SD
Tx, transplantation

encing the selection of the treatment option was CHD. Comparison of the two groups showed that more patients in the SIK group had interventions for CHD ($p$=0.04; Table 1). No difference was detectable regarding time on waiting list and time on dialysis before transplantation. The control group of 11 patients with KTA showed similar characteristics, but with an older age at diagnosis of type 1 diabetes ($p$=0.003) and at transplantation ($p$=0.04), as well as greater duration of pretransplant dialysis ($p$=0.03).

*Donor characteristics* The kidney donors for SPK patients were significantly younger than SIK donors (33.8±11.5 vs 48.8±10.1 years, $p$=0.002). HLA-matches (out of six) between SPK and SIK recipients (1.8±0.9 vs 2.0±0.9, $p$=0.80) and the cold ischaemia time of the kidney (13.8±4.3 vs 12.8±3.0 h, $p$=0.44) did not differ. The characteristics of islet donors and islet isolation outcomes are given in Table 2.

*Complications* Surgical complications during the first 3 months after the intervention in both groups are summarised with regard to complications related to the kidney transplantation and to the pancreas or islet transplantation in Table 3.

The number of patients with surgical complications assignable to the kidney transplantation was the same in both groups, as was the number of patients requiring a revision of the site of kidney transplantation. Most of these complications were due to postoperative bleeding.

There were only two cases of minor liver bleeding without need for surgical revision in islet transplanted patients, whereas in pancreas transplantation 12 patients (48%) suffered complications. Ten (40%) patients in the pancreas transplant group underwent relaparotomy for diagnostic or therapeutic reasons, which is significantly different in comparison to the SIK patients (0%; $p$=0.04). The indications for relaparotomy were bleeding (two), infection (two), intestinal obstruction and volvulus (two), ischaemia (one) and relaparotomy for diagnostic reasons in unclear cases (three).

*Follow-up* Mean postoperative follow-up of all patients was 42 months (range 13–66 months) in the SPK and 38 months (range 12–67) in the SIK group.

There were two primary non-functions in the SIK group, one patient with primary non-function of the islet transplant and one patient with primary non-function of the islet and kidney transplant (retransplanted 2 years after the first trans-

**Table 3** Local complications during the first 3 months after the intervention in the SPK and SIK transplantation groups

| Characteristic | SPK | SIK | *p* value |
|---|---|---|---|
| Total number of patients in each group | 25 | 13 | – |
| Patients with complications (pancreas/islets) | 12 (48) | 2 (15) | 0.19 |
| Patients with complications (kidney) | 5 (20) | 3 (23) | 1.00 |
| Patients with (re)laparotomy because of the pancreas/islet Tx | 10 (40) | 0 (0) | 0.04 |
| Patients with revision because of the kidney transplantation | 2 (8) | 2 (15) | 0.61 |

Values are *n* (%)
Tx, transplantation

**Table 4** Preoperative (0 months) and postoperative (12, 24, 36, 48, 60 months) assessment of glucose control ($HbA_{1c}$) and renal function (GFR estimated by MDRD) in SPK, SIK and KTA transplantation patients

| *t* | Number of patients | | | $HbA_{1c}$ (%) | | | | | GFR (ml $min^{-1}$ 1.73 $m^{-2}$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SPK | SIK | KTA | SPK | SIK | *p* value | KTA | *p* value (KTA vs SIK) | SPK | SIK | *p* value | KTA | *p* value (KTA vs SIK) |
| 0 | 25 | 13 | 11 | 8.7±1.9 | 8.1±1.5 | 0.34 | 8.1±1.1 | 0.71 | 10.4±4.1 | 11.8±6.7 | 0.81 | 9.4±2.1 | 0.48 |
| 12 | 25 | 13 | 11 | 6.0±0.6 | 6.2±0.8 | 0.32 | 9.0±1.9 | 0.0009 | 64.7±14.7 | 53.2±20.2 | 0.09 | 54.5±11.1 | 0.98 |
| 24 | 22 | 9 | 10 | 5.7±0.5 | 6.3±0.7 | 0.01 | 8.5±1.5 | 0.005 | 67.5±17.3 | 51.8±24.5 | 0.09 | 53.2±14.9 | 0.73 |
| 36 | 15 | 8 | 9 | 5.8±0.4 | 6.7±1.0 | 0.03 | 9.1±1.3 | 0.007 | 67.3±12.5 | 49.6±24.0 | 0.06 | 47.6±17.9 | 0.95 |
| 48 | 10 | 5 | 9 | 5.5±0.6 | 6.2±0.5 | 0.11 | 8.8±2.1 | 0.03 | 63.5±28.1 | 49.5±17.2 | 0.25 | 46.1±10.0 | 1.00 |
| 60 | 3 | 1 | 9 | 5.3 | 5.7 | – | 8.4±0.7 | – | 47.9±25.5 | 53.0 | – | 48.5±9.2 | – |

Values are means±SD
Significance was defined as $p<0.01$ (Bonferroni correction applied)
*t*, time in months

plantation). The first transplanted kidney in this patient originated from a 53-year-old marginal organ donor (long hypotensive episode, pulmonary oedema, resuscitation). The second kidney of the same organ donor transplanted in a patient without diabetes also failed to function. There was no case of primary non-function in the SPK group.

One islet–kidney recipient died 1 year after transplantation due to cerebral ischaemia not related to transplantation (confirmed by autopsy).

*Glucose control and stimulated C-peptide response* $HbA_{1c}$ values over time are shown in Table 4. The preoperative values did not differ between the two groups, nor did they differ significantly during follow-up. Importantly, they remained stable over time. Similarly, $HbA_{1c}$ before transplantation was not different between KTA recipients and the two groups with beta cell replacement. In contrast, post-transplant $HbA_{1c}$ levels of the KTA group were higher than the pretransplant levels. During the first 3 years after transplantation $HbA_{1c}$ in patients with KTA was significantly different as compared with patients who received beta cell replacement (SPK or SIK, $p<0.01$). Thereafter, the difference persisted, but due to the low number of patients with a follow-up of longer than 3 years in the SIK group, the difference was no longer significant.

Stimulated C-peptide concentration 1 year after transplantation in the SIK group was ≥0.2 nmol/l in 11 of 13 patients and in 10 of 13 at the end of follow-up (Table 5). In

**Table 5** Time points of beta cell replacement in the SIK group, with stimulated C-peptide concentrations and maximally stimulated glucose levels at different time points after islet transplantation

| Patient | Time of beta cell replacement (months) | Follow-up (months) | Maximally stimulated C-peptide (nmol/l) | | | Maximally stimulated glucose (mmol/l) | | |
|---|---|---|---|---|---|---|---|---|
| | | | After last Tx | 1 year | End of follow-up | After last Tx | 1 year | End of follow-up |
| SIK 1 | 0, 2, 9, 15, 22 | 67 | 3.71 | 1.36 | 1.91 | 7.6 | 16.1 | 8.9 |
| SIK 2 | 0, 0, 26, 39 | 58 | 1.64 | 0.77 | 0.73 | 10.1 | 10.6 | 10.6 |
| SIK 3 | 0, 0, 40 | 57 | 2.66 | 2.20 | 2.14 | 8.1 | 7.4 | 12.7 |
| SIK 5 | 0, 5, 6 | 51 | 1.35 | 1.78 | 1.00 | 10.9 | 5.8 | 12.8 |
| SIK 6 | 0, 11 | 45 | 0.68 | 0.68 | 0.11 | 16.4 | 16.4 | 17.9 |
| SIK 7 | 0 | 40 | 2.96 | 0.24 | 0.21 | 10.6 | 11.8 | 26.7 |
| SIK 8 | 0, 3, 6, 33 | 39 | 1.93 | 2.09 | 1.93 | 10.1 | 10.8 | 10.1 |
| SIK 10 | 0 | 12[a] | 1.57 | 1.02 | 1.02[a] | 9.1 | 5.2 | 5.2[a] |
| SIK 11 | 0 | 21 | 0.87 | 1.26 | 1.26 | 12.9 | 14.9 | 14.9 |
| SIK 12 | 0 | 13 | 0.26 | 0.20 | 0.20 | 14.3 | 15.5 | 15.5 |
| SIK 13 | 0 | 12 | 0.24 | 0.54 | 0.54 | 17.6 | 22.8 | 22.8 |

Islet primary non-function (patients SIK 4, SIK 9) has been excluded
[a] Death of patient before end of follow-up
Tx, transplantation

the representative sample of SPK patients who underwent a meal stimulation test, the stimulated C-peptide levels were significantly higher than in the SIK group at the end of follow-up (mean 2.505±0.762 in the SPK group vs 1.005± 0.735 nmol/l in the SIK group).

Current CGMS measurements in the representative SPK and SIK groups (mean 53.6±23.0 and 59.2±24.2 months after transplantation, respectively) showed less variability of glucose values, particularly of postprandial levels, in the SPK group (Fig. 1).

*Insulin independence* The number of islet transplantations in the SIK group was 28 (mean: 2.2 per patient; Table 2). Initial insulin independence was achieved in five of seven patients who received two ore more islet transplantations, but persisted only in two of them. In contrast, in the SPK group all but one patient remained insulin-free. Insulin independence in all groups 1 year after transplantation was 96 and 31% in SPK and SIK, respectively. The insulin dose required to achieve near-normal glucose levels in SIK patients was half of that needed before transplantation, i.e. 0.56±0.17 and 0.29±0.21 U $kg^{-1}$ $day^{-1}$ before and after transplantation (mean dose during follow-up), respectively.

The amount of insulin needed during follow-up was strongly dependent on the volume of transplanted islets. When the SIK group was divided into patients who received less than 10,000 IEQ/kg in total (mean 4,662±2,660 IEQ/kg) and those treated with more than 10,000 IEQ/kg (mean 23,537±7,363 IEQ/kg), the difference in insulin need (mean during follow-up) was 0.39±0.14 versus 0.08± 0.06 U $kg^{-1}$ $day^{-1}$ ($p$=0.02). However, $HbA_{1c}$ (mean during follow-up) was not significantly different between the two groups (6.2±0.5% in patients with more than 10,000 islets transplanted and 6.3±0.8% in patients with less than 10,000 islets transplanted, $p$=0.87; Fig. 2a,b). The mean $HbA_{1c}$ in the SPK group during follow-up was 5.9±0.5%.

*Hypoglycaemia* In all patients treated with SPK or SIK transplantation, there were no episodes of severe hypoglycaemia (grades II and III) after transplantation, even in SIK patients treated with insulin after transplantation and despite the significantly better blood glucose control (i.e. reduction of $HbA_{1c}$ from 8.4% pre-transplant to 6.3% post-transplant, mean during follow-up). Before transplantation severe episodes of hypoglycaemia had occurred in 10 out of 13 SIK patients.

*Kidney function* The estimated GFR (MDRD) in the three groups is shown in Table 4. The non-significant differences

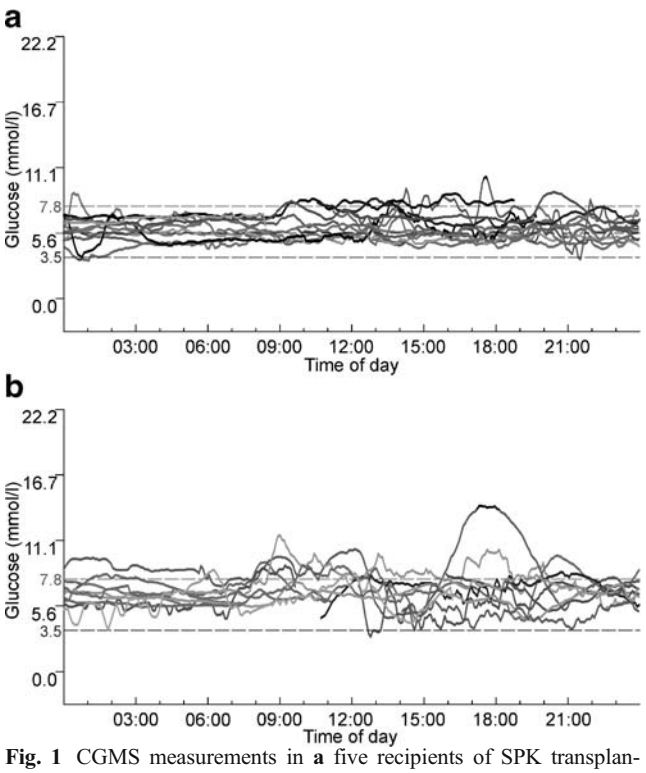


**Fig. 1** CGMS measurements in **a** five recipients of SPK transplantation and **b** five recipients of SIK transplantation at the end of follow-up. The dashed lines represent the limits of normal glucose fluctuation in individuals with no diabetes

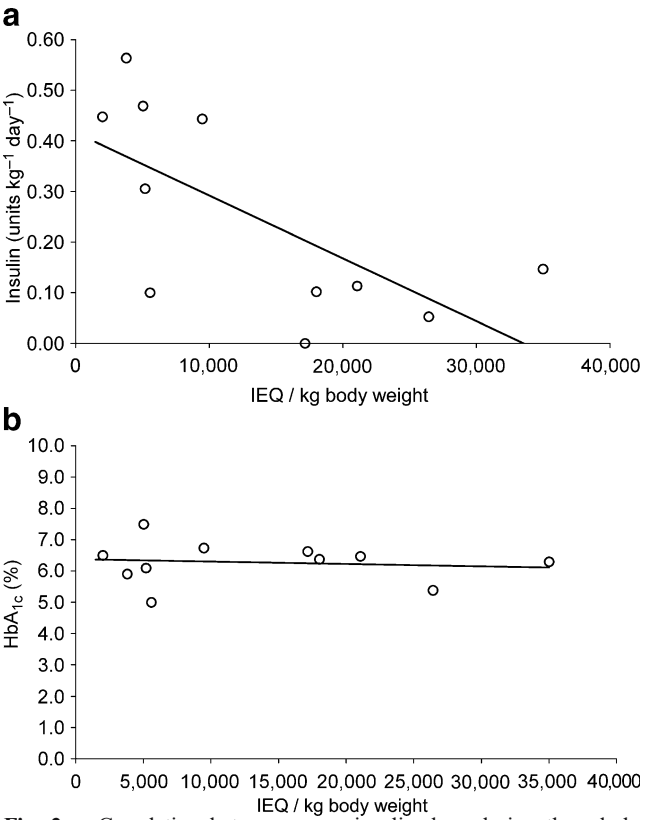


**Fig. 2** **a** Correlation between mean insulin dose during the whole follow-up after transplantation and transplanted IEQ per kg recipient weight in islet recipients. Regression coefficient $r$=−0.731, $p$=0.007. **b** Correlation between mean $HbA_{1c}$ during the whole follow-up after transplantation and transplanted IEQ per kilogram recipient weight in islet recipients. Regression coefficient $r$=−0.138, $p$=0.67

in the estimated GFR between SPK and SIK recipients are best explained by the difference in donor and recipient age (Tables 1 and 2). Linear regression showed that the postoperative GFR was dependent on the age of the kidney donors ($r=-0.54$, $p=0.0007$). There was no difference in kidney function between patients with beta cell replacement (SPK, SIK) and those without (KTA).

*Cardiovascular risk factors during follow-up* Blood pressure, triacylglycerols, total cholesterol and both HDL-and LDL-cholesterol are shown in Table 6. No significant difference was observed between the two groups pretransplant and during the 5 year follow-up period.

*Immunosuppression during follow-up* Prednisone, given to SPK recipients, was tapered to 5 mg/day or less in 76% of patients after 1 year and 91% of patients after 2 years.

*Full cost analysis* The cost of SPK transplantation in our institution was 57,772±30,649 € as compared with 53,693± 8,603 € for SIK and 33,805±16,603 € for KTA. The cost of islet transplantation after SIK was 18,778±302 €. The hospitalisation times for SPK, SIK and KTA were 22±12, 18±7 and 15±9 days, respectively. Patients with islet transplantation after SIK were discharged within 1 day. The cost of SIK transplantation on the basis of 2.2 islet transplantations (mean of this study per patient) would thus amount to 76,227±8,966 €.

## Discussion

This is the first direct single centre comparison of SIK and SPK as treatment for type 1 diabetes mellitus and renal failure. The aim was to compare the outcome of these two treatment options performed at the same institution and followed up by the same team with identical levels of care.

Both transplantation options have become important treatment alternatives to intensive insulin treatment for patients with type 1 diabetes mellitus. Whole-organ transplantation is offered mainly to patients with type 1 diabetes and end-stage renal failure, since pancreas transplantation is reimbursed by the Swiss health care system only for this indication due to the better survival of SPK as compared with KTA patients [14, 15].

**Table 6** Preoperative (0 months) and postoperative assessment of clinical characteristics for SPK and SIK patients

| Clinical characteristics | Time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 12 | 24 | 36 | 48 | 60 |
| Systolic BP (mmHg) | | | | | | |
| SPK | 151±23 | 135±23 | 144±16 | 134±11 | 138±18 | 136 |
| SIK | 146±22 | 134±18 | 133±19 | 137±21 | 146±23 | 162 |
| *p* value | 0.70 | 0.69 | 0.26 | 0.96 | 0.56 | – |
| Diastolic BP (mmHg) | | | | | | |
| SPK | 86±13 | 78±14 | 83±11 | 77±5 | 80±13 | 77 |
| SIK | 84±13 | 68±5 | 78±20 | 71±12 | 84±12 | 82 |
| *p* value | 0.92 | 0.04 | 0.66 | 0.34 | 0.63 | – |
| Triacylglycerol (mmol/l) | | | | | | |
| SPK | 1.7±0.9 | 1.3±0.5 | 1.0±0.4 | 0.9±0.2 | 0.9±0.2 | 0.7 |
| SIK | 1.8±1.1 | 1.5±0.8 | 1.5±0.4 | 1.2±0.2 | 1.6±1.0 | 0.6 |
| *p* value | 0.69 | 0.55 | 0.03 | 0.03 | 0.11 | – |
| Total cholesterol (mmol/l) | | | | | | |
| SPK | 4.4±1.2 | 4.2±1.2 | 3.9±1.0 | 4.1±0.9 | 4.1±0.9 | 1.6 |
| SIK | 5.4±1.4 | 4.9±0.9 | 4.8±1.0 | 4.7±1.0 | 5.5±1.0 | 3.2 |
| *p* value | 0.02 | 0.05 | 0.08 | 0.38 | 0.05 | – |
| HDL-cholesterol (mmol/l) | | | | | | |
| SPK | 1.5±0.5 | 1.5±0.3 | 1.5±0.4 | 1.5±0.5 | 1.5±0.6 | 0.5 |
| SIK | 1.5±0.6 | 1.6±0.5 | 1.5±0.3 | 1.7±0.6 | 1.9±0.3 | 1.6 |
| *p* value | 0.95 | 0.64 | 0.76 | 0.55 | 0.28 | – |
| LDL-cholesterol (mmol/l) | | | | | | |
| SPK | 2.2±0.9 | 2.1±1.0 | 2.1±0.7 | 2.2±0.7 | 2.2±0.6 | 0.8 |
| SIK | 3.0±1.1 | 2.6±0.7 | 2.6±0.9 | 2.5±0.6 | 2.9±1.0 | 1.3 |
| *p* value | 0.03 | 0.08 | 0.20 | 0.48 | 0.07 | – |

Values are means±SD
Significance was defined as $p<0.01$ (Bonferroni correction applied)

Some differences between the two procedures are obvious, e.g. the more invasive character of whole-organ transplantation compared with the transplantation of isolated islets. A randomised trial was not feasible due to inherent differences in the transplantation procedures and associated complications, which favour whole-organ transplantation in younger patients with fewer comorbidities. Therefore, we retrospectively analysed the results of beta cell replacement in both groups. These considerations are reflected by the different demographic findings in the two groups.

The beneficial effect on glucose control has been individually described both for SPK [16] and SIK patients [4]. We were able to demonstrate a significant improvement of $HbA_{1c}$ values after transplantation in both groups, whereas in a group of patients who received KTA $HbA_{1c}$ increased after transplantation, probably due to the immunosuppressive regimen (steroids) in addition to persistent problems in diabetes management.

Post-transplant $HbA_{1c}$ values in the beta cell replacement groups were comparable and remained stable during follow-up. The non-significant difference in $HbA_{1c}$ levels is best explained by elevated postprandial glucose levels in SIK patients as seen in the CGMS measurements. Monnier et al. [17] were able to show that in patients with $HbA_{1c}$ <7.3%, 70% of the $HbA_{1c}$ value is determined by postprandial glucose levels.

However, long-term insulin independence was much lower in the SIK group, with only two of 13 patients being insulin-independent at the end of follow-up (48 and 60 months after transplantation), a result which is in line with the findings of the Edmonton group [18]. A decrease either in mass or function of islets over time after transplantation occurs for different reasons. Apart from impending graft rejection, these include the potentially harmful effects of immunosuppressive drugs at high doses in the portal circulation [19] or failure of sufficient regeneration.

Nevertheless, the remaining islet mass and function—as reflected by a positive C-peptide response in eleven out of 13 patients 1 year after transplantation—is sufficient to maintain glucose control (assessed by $HbA_{1c}$ levels and CGMS measurements) at a near-normal and significantly lower level than pretransplantation for several years at the least. Interestingly, our data show that there was only a marginal benefit in terms of glucose control in those patients who received multiple islet transplantations in contrast to their clear benefit when comparing the amount of exogenous insulin administered. This finding and the non-significant difference in glucose control between SIK and SPK patients despite much higher C-peptide levels and insulin independence in the latter group show that the findings of the DCCT [20, 21] also apply to patients after islet transplantation. Thus even a minor residual beta cell function can significantly improve glycaemic control, provided that patients are intensively treated (continuous subcutaneous insulin infusion or multiple insulin injections). Given the restricted availability of donor organs in our institution, we generally do not repeat islet transplantation to achieve insulin independence, unless endogenous insulin secretion is insufficient to achieve target $HbA_{1c}$ levels. In the present study, this is reflected by the low number of insulin-independent patients (31%) 1 year after transplantation in the SIK group compared with the SPK group. International multicentre data also suggest that even in islet transplantation alone, insulin independence after 1 year cannot be achieved in the majority of patients who undergo transplantation of islets up to three times [22].

One important point in the context of multiple (repetitive) islet transplantations is the cost. In our setting, costs for SIK are lower than for SPK by ~10%, but exceed these if two or more islet transplantations have to be performed. However, these numbers do not take follow-up costs due to complications and/or rehospitalisation into account.

Life-long immunosuppression, which is required for the kidney transplant, is not an additional cost factor or risk factor for major complication in SIK transplantation. The costs of islet transplantation are justified by a much better glycaemic control (without hypoglycaemia) than that achieved in intensive insulin trials [23] or in our control group with KTA.

In contrast to transplantation of isolated islets, transplantation of the whole organ always aims to achieve insulin independence, which can, as demonstrated here, be accomplished in most patients. The price of this benefit, however, is a much more invasive procedure with frequent local complications related to the pancreas transplantation. During the first 3 months after transplantation, 40% of the transplanted patients had to undergo relaparotomy due to local abdominal complications related to the operation. Results published by the European Trial of Immunosuppression in Simultaneous Pancreas Kidney Transplantation (EUROSPK) study group show that repeat laparotomies in the first 3 months after transplantation were performed in 35% of all patients [24]. Large single centre trials show smaller numbers of complications, with the Minnesota group, for example, reporting relaparotomy in just 19% of patients [25]. Compared with a large pancreas transplant centre, our centre is rather small. However, in contrast to these centres, our transplantation programme processed the same number of pancreata for pancreas and islet transplantation, allowing a direct comparison of the two methods with no inherent bias. Furthermore, we sought to prevent loss of function of the transplanted organ in every possible way, which led to more therapeutic and diagnostic relaparotomies, resulting in a high pancreas transplant graft survival of 96% at 1 year, compared with 85% in US pancreas transplants reported to the International Pancreas Transplant Registry [26].

The most common causes of relaparotomies in the SPK group were haemorrhage, intestinal obstruction and infec-

tion. Except for two cases of minor liver bleeding without need for revision or transfusion, there were no local complications related to islet transplantation in the SIK group. Complications and surgical revisions due to the kidney transplantation were comparable in both groups, which suggests that the two groups had similar susceptibility to local complications in general.

Renal function of the transplanted kidney does not seem to be influenced by the choice of one of the two transplantation or immunosuppression options. We were not able to detect a significant difference in renal function between the two groups. The tendency towards a better GFR of the transplanted kidney in the SPK group can be attributed to the significantly lower recipient and donor ages in this group.

Despite a much higher insulin independence rate and younger age in the SPK group, the post-transplant cardiovascular risk profile (blood pressure, lipid profile and glycated haemoglobin) was not significantly different between the two transplant groups.

Immunosuppression was different in the two groups. Whereas in the SIK group, immunosuppression was carried out according to the Edmonton protocol using sirolimus and low-dose tacrolimus, and by strictly avoiding steroids, the SPK group received a combination therapy of tacrolimus, mycophenolate mofetil and (initially) steroids. In solitary kidney transplantations, the latter regimen seems to have advantages compared with the sirolimus–tacrolimus combination in terms of graft function and graft survival [27, 28]. However, this was not observed in our series, since kidney function over time proved to be very stable. With regard to glucose control, a prospective study did not reveal any different effects of mycophenolate mofetil and sirolimus in SPK recipients [29].

A limitation of this study is its retrospective and non-randomised character and the relatively low number of patients involved. The major advantage, however, is that both patient groups were operated at the same institution and follow-up was performed by the same team. The collection of follow-up data has a high level of completeness ($HbA_{1c}$ levels obtained in 87.6%, insulin dosage in 98.2%, creatinine levels in 100% of cases).

In summary, this study demonstrates that SPK transplantation results in a much higher insulin independence at the cost of more surgical complications as compared with SIK transplantation, with glycaemic control comparable in both groups. Endogenous insulin production by transplanted islets combined with optimal insulin therapy seems to be sufficient for maintenance of near-normal glucose levels and disappearance of severe hypoglycaemia, which we consider to be the primary objectives of islet transplantation. Particularly in the face of organ shortage, these findings may lead to a new paradigm in islet transplantation, where the primary goal is not necessarily to achieve the same rate of insulin independence as in whole-organ transplantation, but to achieve a significant improvement in glucose control through a much less invasive procedure.

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