Glycemic Control in Simultaneous Islet-Kidney Versus Pancreas-Kidney Transplantation in Type 1 Diabetes: A Prospective 13-Year Follow-up

OBJECTIVE
In patients with type 1 diabetes and end-stage renal disease, combined transplantation of a kidney together with a pancreas or isolated pancreatic islets are options to improve glycemic control. The aim of this study was to compare their long-term outcome with regard to metabolic control and surgical complication rate, as well as function of the transplanted kidney.

RESEARCH DESIGN AND METHODS
We conducted a prospective cohort study in consecutive patients receiving either a pancreas or islet transplant simultaneously with or after kidney transplantation (simultaneous pancreas-kidney [SPK]/pancreas-after-kidney [PAK] or simultaneous islet-kidney [SIK]/islet-after-kidney [IAK] transplantation).

RESULTS
Ninety-four patients who had undergone SPK/PAK transplantation were compared with 38 patients who had undergone SIK/IAK transplantation over a period of up to 13 years. HbA1c levels declined from $7.8 \pm 1.3\% (62 \pm 14 \text{ mmol/mol})$ to $5.9 \pm 1.1\% (41 \pm 12 \text{ mmol/mol})$, and from $8.0 \pm 1.3\% (64 \pm 14 \text{ mmol/mol})$ to $6.5 \pm 1.1\% (48 \pm 14 \text{ mmol/mol})$, respectively, in the SPK/PAK and SIK/IAK groups ($P < 0.001$ for both) and remained stable during follow-up, despite a reduction in the rate of severe hypoglycemia by >90%. The 5-year insulin independence rate was higher in the SPK/PAK group (73.6 vs. 9.3% in the SIK/IAK group), as was the rate of relaparotomy after transplantation (41.5 vs. 10.5% in the SIK/IAK group). There was no difference in the rate of kidney function decline.

CONCLUSIONS
During a long-term follow-up, SPK/PAK transplantation as well as SIK/IAK transplantation resulted in a sustained improvement of glycemic control with a slightly higher glycated hemoglobin level in the SIK/IAK group. While insulin independence is more common in whole-organ pancreas recipients, islet transplantation can be conducted with a much lower surgical complication rate and no difference in kidney function decline.
Both the transplantation of isolated islets of Langerhans as well as the transplantation of whole-organ pancreas are treatment options in the care of patients with type 1 diabetes. However, there are few data regarding their long-term outcome, in particular when compared with each other.

Whereas pancreas transplantation has been conducted for almost 50 years (1), islet transplantation emerged as an alternative to whole-organ transplantation mainly after results of consistent insulin independence using a steroid-free immunosuppression protocol were published in 2000 (2), although metabolic effects of successful islet transplantation had already been described (3).

Both transplantation options can be conducted alone or in combination with a kidney. Whereas simultaneous pancreas-kidney (SPK) transplantation is an intervention with proven benefits in terms of survival (4), conflicting results in pancreas transplantation alone have been published (5,6).

By providing a source of endogenous insulin secretion, both transplantation options aim at improving glycemic control. Yet, whereas insulin independence is routinely achieved in patients who have undergone pancreas transplantation and is still present in 60–70% of patients 5 years after transplantation (7), recipients of islet transplantation need more than one transplantation to achieve insulin independence in most cases and insulin independence is lost in >70% of patients after 2 years (8). On the other hand, the complication rate is high in patients who have undergone pancreas transplantation, with >40% of patients undergoing relaparotomy during the first 3 months (9), whereas the laparotomy rate in patients who have undergone islet transplantation is as low as 3% (8).

Data on the outcomes of SPK transplantation compared directly with simultaneous islet-kidney (SIK) transplantation are rare. We reported a 5-year follow-up of patients who had undergone SPK transplantation versus those who had undergone SIK transplantation (10), and a comparison of pancreas versus islet transplantation alone was presented recently, but that study (11) did not include information on glycemic control.

The aim of this study was to compare SPK and SIK transplantation conducted at a single center with regard to glycemic control, transplantation-related complications, as well as the function of the transplanted kidney.

RESEARCH DESIGN AND METHODS

Study Design
All patients who underwent SPK, pancreas-after-kidney (PAK), SIK, or islet-after-kidney (IAK) transplantation at the University Hospital Zurich between 1 January 2000 and 31 December 2013 were included. Study entry was defined as the date of transplantation. Follow-up ended on 31 December 2013 or earlier if either of the following occurred: death of the patient or retransplantation of a kidney, of a pancreas or of islets after initial pancreas transplantation (but not retransplantation of islets in patients receiving initial islet transplantation).

The study protocol was reviewed and approved by members of the board of trustees of the University Hospital of Zurich Transplantation Center. After 2008, patients were simultaneously included in the Swiss Transplant Cohort Study. Written informed consent was obtained from study participants prior to surgery/intervention.

Patient Selection for Transplantation
Patients with type 1 diabetes and end-stage renal failure with need for dialysis treatment who were referred to our institution for the evaluation of possible renal transplantation were considered for combined transplantation. Malignant disease, chronic infection, advanced heart disease, severe liver damage, or noncompliance with treatment were general contraindications for transplantation. Patient selection for one of the two protocols of combined transplantation was performed after careful evaluation of possible advantages and disadvantages, with special regard to age and comorbidities. Older patients with many comorbidities—in particular cardiovascular comorbidities—who were considered to be at higher risk of intraoperative complications were preferentially assigned to undergo the less invasive procedure of islet transplantation, whereas younger and healthier patients were offered both modalities.

Assessment of Diabetes-Related Complications, Hypoglycemia, and Cardiovascular Risk Factors

Retinopathy was defined according to the diagnosis made by ophthalmological examination. Peripheral neuropathy was defined by clinical examination, using the Michigan Neuropathy Screening Instrument (12), monofilament pressure sensation, and electrodiagnostic testing in atypical cases. Autonomic neuropathy was diagnosed by the history and clinical examination, which included computer analysis of heart rate variability (ProSciCard; CPS GmbH, Wetzlar, Germany) in atypical cases.

Severe hypoglycemia was defined as a hypoglycemic episode requiring assistance or leading to loss of consciousness.

Macrovascular disease was assessed by patient history, physical examination, and cardiographic results, including electrocardiography, chest X-ray, echocardiography, and coronary angiography in all patients.

Organ Procurement and Surgical Procedures

Kidneys and pancreata were obtained from brain-dead multiorgan 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 ABO compatibility was required. Organs of donors were preferentially allocated to recipients of a comparable age.

The transplantation of the pancreas was performed heterotopically through 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 exocrine enteric drainage.

Preparation and transplantation of the pancreatic islets were performed as previously described (13). Transplanted islets were not cultured before transplantation. Islet transplantation was conducted by the open approach if performed together with a kidney transplantation, and by the tranhepatic percutaneous approach in all other cases. Islet volume is given as islet equivalents (IEQ) (14). The islet transplantation protocol was submitted to the ethics committee of the University Hospital Zurich, and written informed
consent was obtained from each patient. Insulin treatment was always continued after islet transplantation for at least 3 months (whenever possible with insulin pump therapy) to ensure optimal conditions for islet engraftment.

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.

Heparin was administered in all patients starting 4 h after transplantation (10,000 units/day). In addition, 70 units heparin/kg recipient weight (but not >5,000 units in total) were added to islet preparations prior to infusion.

Immunosuppression
In the SPK group, a regimen with tacrolimus (Astellas Pharma, Villars-sur-Glâne, Switzerland) (15) and mycophenolate mofetil (Roche Pharma, Basel, Switzerland) (16), as well as prednisone (Streuli Pharma, Uznach, Switzerland) was used. Induction therapy was performed initially with basiliximab (Novartis Pharma, Basel, Switzerland), and after 2012 with thymoglobulin (Sanofi, Paris, France) (17). Target long-term trough levels for tacrolimus were 10–15 μg/L. Mycophenolate mofetil was administered after weight adaptation twice daily in doses of 720–1,440 mg.

In the SIL group, immunosuppression was carried out with tacrolimus and sirolimus (Wyeth Pharma, Zug, Switzerland), according to the Edmonton protocol (2). The target long-term trough levels were 7–10 μg/L for sirolimus and 3–6 μg/L for tacrolimus. Sirolimus was later changed to mycophenolate mofetil because of the high rate of side effects reported for sirolimus (8). Induction therapy was performed initially with daclizumab (Roche Pharma), and after 2012 with thymoglobulin (Sanofi) (18) or basiliximab (Novartis Pharma) for retransplantation.

For patients receiving pancreas or islet transplantation after kidney transplantation (PAK or IAK), immunosuppression was similar compared with simultaneous transplantation, with the exception of induction therapy, where thymoglobulin was replaced by basiliximab.

Follow-up
During follow-up, pancreas or islet transplant function was assessed by HbA1c measurement and the need for exogenous insulin. In SIL/IAK transplant recipients, C-peptide secretion was measured during a mixed-meal tolerance test (6 kcal/kg body wt, energy sources: 54% carbohydrates, 29% fat, 17% protein; measurements every 30 min for 180 min) at least once a year after transplantation. Because of the high rate of insulin independence, C-peptide was not routinely measured after SPK transplantation. Renal function was assessed by measurement of serum creatinine and glomerular filtration rate (GFR) estimated by the Chronic Kidney Disease Epidemiology Collaboration formula (19). Patients were seen at least every 6 months for evaluation of transplant function and adverse events. For assessment of cardiovascular risk, blood pressure, and levels of triacylglycerol, total cholesterol, and both HDL and LDL cholesterol were measured, in addition to assessment of glycemic 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. Insulin therapy was initiated when HbA1c levels increased repeatedly to >6.0% (42 mmol/mol) or the fasting glucose level was repeatedly measured as >7.0 mmol/L, starting with low-dose basal insulin (4–8 units). The amount of insulin needed was documented by calculating mean daily insulin dosages from patient logs.

Statistical Analysis
Data are described as the mean ± SD or relative frequencies. For the analysis of categorical frequency data, the χ² and Fisher exact probability procedures were applied. For the comparison of continuous variables in two independent groups, Student t tests and Mann-Whitney U tests were used. A value of P < 0.05 was considered to be significant. The Bonferroni correction was applied to account for multiple comparisons, and the adapted level of significance (α'') is indicated when the Bonferroni correction was used. Multiple linear regression was used for the testing of correlations. For the calculation of insulin independence rate at 5 years, the Kaplan-Meier estimator and log-rank test were used. All calculations were performed using SPSS Statistics software version 22 (IBM, Armonk, NY).

RESULTS
Baseline Characteristics
Baseline characteristics of both patient groups are summarized in Table 1. Patients receiving SIL/IAK transplantation were significantly older and had a longer duration of diabetes before transplantation. Diabetes-related complications were common in patients before transplantation (Table 2). In addition to end-stage renal disease (present in all patients), >95% of patients experienced...

| Table 1—Baseline and transplantation-related characteristics of patients included in the study |
|---------------------------------|------------------|------------------|------------------|
|                                | SPK/PAK transplant group | SIL/IAK transplant group | P value* |
| Gender (female) (%)            | 47.9              | 50.0             | 0.83            |
| Age at transplantation (years) | 44.2 ± 7.6        | 51.8 ± 9.0       | <0.001          |
| Age at diagnosis (years)       | 12.3 ± 7.0        | 14.7 ± 10.0      | 0.28            |
| Diabetes duration before transplantation (years) | 32.1 ± 8.2 | 37.0 ± 11.0 | 0.02 |
| Follow-up after transplantation (years) | 5.6 ± 3.8 | 6.4 ± 3.9 | 0.36 |
| Time on waiting list (months)  | 11.3 ± 9.3        | 17.3 ± 14.7      | 0.02            |
| Donor age (years)              | 32.6 ± 12.1       | 53.4 ± 8.1       | <0.001          |
| Donor female sex (%)           | 66.6              | 68.9             | 0.58            |
| Donor BMI (kg/m²)              | 23.2 ± 3.2        | 25.9 ± 2.7       | <0.001          |
| Cold ischemia time (minutes)   | 561.2 ± 180.6     | 325.6 ± 81.6     | <0.001          |
| Transplants (n)                | NA                | 2.1 ± 1.3        |                 |
| Islets/kg body wt/transplantation (n) | NA            | 8,839 ± 7,454   |                 |
| IEQ/kg body wt/transplantation (n) | NA              | 11,408 ± 10,380 |                 |

Data are provided as mean ± SD, unless otherwise indicated. NA, not applicable. *Calculated for comparison between groups (Mann-Whitney U test).
Follow-up of Islet vs. Pancreas Transplantation

Diabetes Care

Heart disease was present in ~50% of patients, with a tendency toward a higher frequency in SIK/IAK recipients ($P = 0.06$). Known cerebrovascular disease was present in 15–25% of patients, and peripheral vascular disease in ~50% of all patients; 28.3% of SPK/PAK recipients and 36.8% of SIK/IAK recipients were smokers (not significant).

A total of 68.6% of SIK/IAK transplant recipients and 76.9% of SPK/PAK transplant recipients had experienced at least one episode of severe hypoglycemia in the preceding year (not significant).

**Transplantation-Related Characteristics**

Transplantation-related characteristics are described in Table 1. Time on the waiting list before transplantation for SIK/IAK transplant recipients was 6 months longer than for SPK/PAK transplant recipients ($P = 0.02$). Donors of organs for SIK/IAK transplant recipients were ~20 years older than SPK/PAK transplant organ donors; this was true for pancreas donors of SPK/SIK transplantation (age difference of 20.3 years) as well as organ donors for transplantation after kidney transplantation (i.e., PAK/IAK transplantation). Islet recipients received on average 2.1 ± 1.3 transplantations per patient, with a mean of 11,408 ± 10,380 IEQ/kg body wt.

In the whole-organ transplant groups, only one patient received a pancreas transplantation that was not simultaneous, but received a PAK transplantation. In the islet transplant group, 15 patients received IAK transplantation.

Retransplantation leading to exclusion from the study according to the study protocol was performed in a total of seven patients: there was no kidney retransplantation, but two patients received pancreas retransplantation and five patients received islet retransplantation after an initial pancreas transplantation. These retransplantations occurred after a mean time of 3.2 ± 2.0 years.

**Table 2—Diabetes related complications and history of cardiovascular disease of patients included in the study**

<table>
<thead>
<tr>
<th></th>
<th>SPK/PAK transplant group</th>
<th>SIK/IAK transplant group</th>
<th>$P$ value*</th>
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<td>Nonproliferative</td>
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</tr>
<tr>
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<td>13.2</td>
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<td>Cerebrovascular disease</td>
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<td>76.3</td>
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<tr>
<td>Asymptomatic</td>
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<tr>
<td>Transient ischemic attack</td>
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<td></td>
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<tr>
<td>Stroke</td>
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<tr>
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<tr>
<td>PCI</td>
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<td>5.3</td>
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<tr>
<td>Ulceration/gangrene</td>
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<td>2.6</td>
<td></td>
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<tr>
<td>Amputation</td>
<td>16.1</td>
<td>21.1</td>
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Data are provided as percentage. PCI, percutaneous intervention. *Calculated for comparison between groups ($\chi^2$ test).

**Insulin Independence and Glycemic Control**

Insulin independence was significantly higher at 5 years for SPK/PAK transplant (73.6%) compared with 9.3% for SIK/IAK transplant (Supplementary Fig. 1) ($P < 0.001$). Nonetheless, in both groups a significant decrease in HbA$_{1C}$ level was observed 1 year after transplantation compared with the last HbA$_{1C}$ level measured before transplantation (Fig. 1). HbA$_{1C}$ levels decreased in the SPK/PAK transplant group from 7.8 ± 1.3% (62 ± 14 mmol/mol) to 5.9 ± 1.1% (41 ± 12 mmol/mol), and in the SIK/IAK transplant group from 8.0 ± 1.3% (64 ± 14 mmol/mol) to 6.5 ± 1.1% (48 ± 12 mmol/mol), respectively ($P < 0.001$ for both, $n = 123$). HbA$_{1C}$ levels remained stable in both groups after transplantation (mean HbA$_{1C}$ level during follow-up 5.8 ± 0.8% [40 ± 9 mmol/mol] and 6.7 ± 1.0% [50 ± 11 mmol/mol] for SPK/PAK and SIK/IAK transplant groups, respectively), with a significantly lower value (compared with pretransplantation) until year 6 (SPK/PAK transplant $P = 0.001$, $n = 31$) and year 7 (SIK/IAK transplant $P = 0.002$, $n = 14$), respectively (Bonferroni correction applied, $\alpha' = 0.004$). In both groups, there was no time point after transplantation when HbA$_{1C}$ level rose significantly compared with year 1 after transplantation. When compared directly, the HbA$_{1C}$ level was lower in the SPK/PAK transplant group compared with the SIK/IAK transplant group at years 2–4 and 6–8 after transplantation (Bonferroni correction applied, $\alpha' = 0.004$).

The mean HbA$_{1C}$ level as well as the last HbA$_{1C}$ level measured during follow-up in patients with a total follow-up of >10 years was not different compared with those with a shorter follow-up time. In the SPK/PAK transplant group, the mean and last HbA$_{1C}$ levels were 5.8 ± 0.8% [40 ± 9 mmol/mol] and 5.7 ± 0.8% [39 ± 9 mmol/mol] for patients with a follow-up time of <10 years, and 5.5 ± 0.4% [37 ± 4 mmol/mol] and 5.4 ± 0.5% [36 ± 6 mmol/mol] for patients with a follow-up time of >10 years (not significant). In the SIK/IAK transplant group, these values were 6.7 ± 1.1% [50 ± 12 mmol/mol] and 6.8 ± 1.3% [51 ± 14 mmol/mol] for a follow-up time of <10 years, and 6.5 ± 0.8% [48 ± 9 mmol/mol] and 6.6 ± 1.2% [49 ± 13 mmol/mol] for a follow-up time of >10 years (not significant).
In the SIK/IAK transplant group, C-peptide secretion was measured at 3, 6, and 12 months after transplantation during a mixed-meal tolerance test (and yearly afterward) (Supplementary Fig. 2). There were three patients without C-peptide response after transplantation in this group (defined as a C-peptide level of <0.1 nmol/L). The highest level of the maximally stimulated C-peptide level during the post-transplant period was 1.34 ± 1.10 nmol/L, and the last value measured during follow-up was 1.12 ± 1.01 nmol/L.

**Kidney Function**

Kidney function levels 1 year after combined transplantation were 70.4 ± 22.7 and 50.0 ± 20.4 mL/min, respectively, in the SPK and SIK transplant groups. Whereas the GFR did not differ between the two groups before renal transplantation, it was significantly different 1 year after transplantation (P < 0.001). However, the decline in renal function of the transplanted kidney after SPK or SIK transplantation was not different between the two groups (Fig. 2) at any time point during follow-up (Bonferroni correction applied, α' = 0.004), with a decline of calculated GFR at year 13 after transplantation of −9.5 ± 23.3 mL/min (SPK transplant group) and −13.3 ± 13.8 mL/min (SIK transplant group) (not significant). The percentages of patients with a change in CKD stage during follow-up were only 16.3% (SPK transplant group) and 8.1% (SIK transplant group) (not significant).

In line with HbA1c values, there was also no difference in kidney function at any time during follow-up between patients with a long (>10 years) and short (<10 years) follow-up time, when assessed separately for the SPK/PAK and SIK/IAK transplant groups.

**Insulin Requirement and Occurrence of Severe Hypoglycemia After Transplantation**

Whereas the amount of insulin needed for diabetes therapy was not different between the two groups before transplantation (>0.5 units/kg body wt), it differed significantly afterward (Fig. 3A and Supplementary Fig. 3). The insulin dosage could be decreased in the SPK/PAK transplant group by >80% (with most patients being insulin independent), but only by <20% in the SIK/IAK transplant group (mean during follow-up). However, the rate of severe hypoglycemia, which was high and not different in both groups before transplantation (346 ± 445 per 100 patient-years in the whole cohort), dropped significantly to 4.5 ± 15.1 and 11.1 ± 15.2 per 100 patient-years in the SPK/PAK and SIK/IAK transplant groups, respectively (Fig. 3B).

**Procedure-Related Complication Rate, Immunosuppression**

In the SPK/PAK transplantation group, the implanted pancreas had to be explanted in 9.6% of patients (9 of 94 patients) because of complications. These complications included bleeding (two cases) and vascular complications (thrombosis, 7 cases). A total of 39 patients (41.5%) in this group underwent early (within 3 months) laparotomy, with more than 1 laparotomy performed in some patients (45 laparotomies in total) (Fig. 3C). The complications leading to early laparotomy included bleeding (13 cases), thrombosis (7 cases), ileus/volvulus (8 cases), infection/pancreatitis (11 cases), and others (2 cases), as well as complications related to the transplanted kidney (4 cases). In contrast, there were only four patients with a need for relaparotomy in the SIK/IAK transplant group (10.5%)

**Figure 1**—HbA1c level (as % [mmol/mol]) after SPK/PAK or SIK/IAK transplantation before (“0”) and after transplantation. n, number of patients observed at a particular time point after transplantation. *P < 0.004 (Mann-Whitney U test, Bonferroni correction applied, α' = 0.004)

**Figure 2**—Change of calculated GFR (mL/min/1.73 m2) after SPK or SIK transplantation. n, number of patients observed at a particular time point after transplantation.
patients with major bleeding at the site of hepatic vein puncture, and two patients with a need for relaparotomy related to the transplanted kidney. In contrast with the difference in total relaparotomy rate, there was no difference in the relaparotomy rate related to the kidney transplantation in the SPK and SIK transplant groups (4.4% and 5.3%, respectively) (not significant).

There was one case of death early after IAK transplantation due to cardiac arrest in a patient with a known history of coronary, cerebral, and peripheral vascular disease after the development of intrathoracic hemorrhage following accidental puncture of an intercostal artery during transhepatic puncture of the portal vein. Immunosuppression with glucocorticoid therapy (prednisone) was conducted in pancreas transplant recipients, but steroids were tapered off as soon as possible. Three years after transplantation, 13.3% of pancreas transplant recipients were receiving prednisone treatment, with 2.7% of patients receiving a dosage higher than 5 mg daily. From year 3 to year 13, the mean percentage of patients receiving therapy with steroids was 8.6 ± 3.8%, with 1.4 ± 1.9% of patients receiving >5 mg of prednisone daily. The steroid dosage did not correlate significantly with HbA1c level at any time point during follow-up.

The induction therapy drug was changed to thymoglobulin in 2012, and 10 patients receiving pancreas transplantation and 4 patients receiving islet transplantation were treated with thymoglobulin.

Cardiovascular Risk Factors, Patient Survival

BMI, blood pressure, and serum lipid levels were compared before and after transplantation (Supplemental Table 4). BMI was significantly higher in SIK/IAK transplant recipients before, but not after, transplantation; BMI was significantly reduced after transplantation in this group, but not in the SPK/PAK transplant group. Both systolic and diastolic blood pressure declined significantly after transplantation in both groups, with a lower diastolic blood pressure in the SIK/IAK transplant group.

The 10-year patient survival rate was higher in the SPK/PAK transplant group compared with the SIK/IAK transplant group (88.5% vs. 65.4%, respectively) (P = 0.004).

CONCLUSIONS

This study is the first prospective cohort study directly comparing the outcome of patients undergoing pancreas or islet transplantation (simultaneously with or after a kidney transplantation) during a long-term follow-up duration of >10 years.

There are differences between the two treatment options that preclude a randomized trial in order to compare the two methods within similar patient groups (e.g., the more invasive character of whole-organ transplantation, which favors whole-organ transplantation in younger patients with fewer comorbidities). This is reflected by the demographic characteristics presented in this study. SPK/PAK transplant recipients were younger, the duration of diabetes was shorter, and the number of diabetes-related complications and cardiovascular disease cases tended to be lower in this group.

The high rate of insulin independence in whole-organ transplant recipients is comparable to the results of current analyses of the International Pancreas Transplant Registry (7). If insulin independence is the aim of islet transplantation, multiple islet infusions are common (8). However, the aim of our transplantation program in double organ transplant recipients is to achieve long-term glucose stability, providing protection from further organ damage caused by hyperglycemia (in particular, deterioration of the function of the transplanted kidney) without the occurrence of severe hypoglycemia. This was achieved in both groups after transplantation, with a reduced number of patients with severe hypoglycemia per year compared with the situation before transplantation, but also compared with patients treated with intensified insulin therapy (20). C-peptide levels remained stable during the first years after islet transplantation, with some decline after year 6. Sustained positive C-peptide response itself may be of importance regarding diabetes-associated complications, given the increasing evidence of the positive effects of C-peptide regarding vascular, renal, and nerve dysfunction (21–23).

Both groups showed an HbA1c concentration that was lower than what was shown in patients treated with intensified insulin therapy (20,24), despite an...
insulin dosage in islet recipients after transplantation that was not significantly lower compared with that before transplantation. However, the transplanted islet mass seems sufficient to provide enough insulin to compensate for inadequately injected amounts of insulin to ensure good glycemic control without severe hypoglycemia. Further, the difference in insulin need before and after transplantation may be underestimated since the insulin requirement before transplantation is reduced because of renal failure, at least in patients with simultaneous transplantation (25).

Prednisone was used in pancreas transplant recipients, but since it could be tapered off in most patients during the first 2–3 years of follow-up or at least could be reduced to low dosages, a relevant impact on glycemic control is unlikely. Published data on induction therapy suggest that induction therapy with thymoglobulin is superior compared with other options (17,18). In our cohort, thymoglobulin induction therapy was only started in 2012; therefore, protocol changes in induction therapy were not influencing long-term outcome.

When assessed 1 year after combined transplantation, renal function was significantly lower in SIK transplant recipients compared with SPK transplant recipients, which is most probably attributable to differences in donor age (26). It should be noted that there was no difference in the rate of decline of renal function between the two groups. In a recent study (27), SPK transplantation has been shown to preserve long-term kidney graft function better than transplantation of a kidney alone. When compared with this study, and supporting its findings, our data in SPK (and SIK) transplant recipients as well as retrospectively collected data on patients receiving kidney transplantation alone display similar results regarding HbA1c levels and the rate of kidney function decline (Supplemental Table 5).

The high relaparotomy rate early after transplantation in SPK/PAK transplant recipients was similar to the rate that was reported recently by Page et al. (9). In contrast to the overall relaparotomy rate, the number of laparotomies that were caused by complications at the site of the kidney transplantation was not different between groups, indicating that the transplantation of the pancreas was the main reason for an increased complication rate in the whole-organ transplantation group.

As expected, the 10-year mortality rate was significantly higher in the SIK/IAK transplant group. A variety of factors may have contributed to this difference. First, SIK/IAK transplant patients were >7 years older. The comparison of similar age categories as assessed by this study within the general population in Switzerland shows an increased mortality (2.3-fold). Further, the tendency toward an increased prevalence and severity of cardiovascular disease may have reduced survival in the SIK/IAK transplant group. In the whole cohort, patients with coronary heart disease exhibited a significantly higher mortality rate than those without coronary heart disease (10-year patient survival rate 65.5% vs. 84.7%, respectively; P = 0.03). Finally, the difference in diabetes duration before transplantation may have contributed independently to the increased mortality in the SIK/IAK transplant group.

The main advantages of this study are the relatively high number of patients, the length of follow-up, and the interdisciplinary care for the patients by the same team during follow-up.

There are some limitations of this study. In addition to the heterogeneous baseline characteristics, there were also differences between the donor and transplantation-related characteristics (e.g., immunosuppression). Further, the study does not include a control group of patients with type 1 diabetes who had undergone renal transplantation, but no islet replacement (pancreas or islet transplantation). Because of the advantages of a combined transplantation, isolated kidney transplantation in these patients is performed very rarely (e.g., if the organ is provided by a living donor). However, even in these cases a pancreas or islet transplantation is conducted subsequently in almost all patients. We previously reported (10) the results of a cohort of patients with type 1 diabetes and kidney transplantation alone, but these transplantations were mostly conducted before the year 2000, which impairs direct comparison (Supplemental Table 5). However, it should be noted that glycemic control was worsening in most of these patients after transplantation, probably due to the negative effects of immunosuppressive medication.

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