Preserved insulin secretion and kidney function in recipients with functional pancreas grafts 1 year after transplantation: a single-center prospective observational study

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Abstract

Objective: Successful simultaneous pancreas and kidney transplantation (SPK) or pancreas transplantation alone (PTA) restores glycemic control. Diabetes and impaired kidney function are common side effects of immunosuppressive therapy. This study addresses glucometabolic parameters and kidney function during the first year.

Methods: We examined 67 patients with functioning grafts (SPK $n=30$, PTA $n=37$) transplanted between September 2011 and November 2016 who underwent repeated oral glucose tolerance tests (OGTTs) 8 and 52 weeks after transplantation. Another 19 patients lost their graft the first year post-transplant and 28 patients did not undergo repeated OGTTs and could not be studied. All patients received ATG induction therapy plus tacrolimus, mycophenolate and prednisolone. Glomerular filtration rate was measured before and 8 and 52 weeks after transplantation by serum clearance methods.

Results: From week 8 to 52 after transplantation, mean fasting glucose decreased (SPK: 5.4 ± 0.7 to 5.1 ± 0.8 mmol/L, PTA: 5.4 ± 0.6 to 5.2 ± 0.7 mmol/L; both $P < 0.05$), and also 120-min post-OGTT glucose (SPK: 6.9 ± 2.9 to 5.7 ± 2.2 mmol/L; $P = 0.07$, PTA: 6.5 ± 1.7 to 5.7 ± 1.2 mmol/L; $P < 0.05$). Fasting C-peptide levels also decreased (SPK: 1500 ± 573 to 1078 ± 357 pmol/L, PTA: 1210 ± 487 to 1021 ± 434 pmol/L, both $P < 0.005$). Measured GFR decreased from enlistment to 8 weeks post transplant in PTA patients (94 ± 22 to 78 ± 19 mL/min/1.73 m²; $P < 0.005$), but did not deteriorate from week 8 to week 52 (SPK: 55.0 ± 15.1 vs 59.7 ± 11.3 mL/min/1.73 m²; $P = 0.19$, PTA: 76 ± 19 vs 77 ± 19 mL/min/1.73 m²; $P = 0.74$).

Conclusion: Glycemic control and kidney function remain preserved in recipients with functioning SPK and PTA grafts 1 year after transplantation.

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Introduction

Simultaneous pancreas and kidney (SPK) transplantation has become an established treatment for patients with type 1 diabetes and end-stage kidney disease (1). Pancreas transplantation alone (PTA) is offered to selected patients with life-threatening brittle diabetes (2, 3).

Successful pancreas transplantation (PTX) has several advantages: restoration of normal blood glucose, insulin independence and reversal of hypoglycemic unawareness, the latter can be of crucial importance for selected patients. PTX may also have beneficial effects on the progression of diabetic nephropathy, retinopathy, neuropathy and atherosclerotic cardiovascular disease (4). Advances in both surgical technique and immunosuppressive therapy have improved long-term results after PTX, but the results are still inferior to other solid abdominal organ transplantations (5), mainly due to surgical complications and rejections (6). Immunosuppressive therapy may have diabetogenic effects. Steroids stimulate gluconeogenesis and glycogenolysis, increase hepatic glucose production and induce peripheral insulin resistance (7) while calcineurin inhibitors (CNIs) may reduce insulin secretion (8, 9). Furthermore, CNIs may deteriorate kidney function due to their nephrotoxic effect. PTA recipients who already have developed diabetes nephropathy may experience additional risk for renal failure. On the other hand, successful PTA is associated with restoration of normal blood glucose which could counteract diabetes-associated progression of kidney injury.

In order to improve our understanding of glucose metabolism and kidney function after pancreas transplantation, we assessed parameters of insulin secretion and action together with renal function 8 and 52 weeks after successful SPKs and PTAs performed at our center.

Subjects and methods

This single-center prospective observational study included 114 consecutive Caucasian patients who underwent PTX in Norway from September 2012 till November 2016.

Recipients who lost their graft during the first year after transplantation ($n=19$) were excluded (Fig. 1: Flow chart). Ninety-five recipients (SPK $n=47$, PTA $n=48$) had a well-functioning pancreas grafts 1 year after transplantation without use of insulin or other glucose-lowering drugs. Sixty-seven recipients were evaluated with repeated oral glucose tolerance tests (OGTTs) at

Figure 1

Flow chart of patient selection in the study.

week 8 and 52 after transplantation and were included in the analysis. Twenty-eight patients did not perform these investigations due to interfering conditions such as infection, acute rejection episodes or were in isolation as antibiotic-resistant bacteria were detected.

All recipients received pancreas transplants with duodeno-duodenal exocrine drainage and systemic venous drainage to the inferior cava vein by an iliac allograft vein as an elongation of the portal vein (10). Patients with type 1 diabetes mellitus (DM) and measured GFR (mGFR) below 20 mL/min/1.73 m² were listed as SPK candidates while patients with type 1 DM, 'Brittle-diabetes' and mGFR > 30 mL/min/1.73 m² were listed as candidates for PTA. Data for the two recipient groups are presented separately since they were recruited from two different patient pools.

Thirty PTX recipients underwent simultaneous pancreas and kidney transplantation (SPK) while 37 underwent PTA. Out of the 37 PTA patients, two patients had pancreas transplantation after kidney transplantation, two patients had pancreas transplantation after islet transplantation and one patient had pancreas re-transplantation after SPK transplantation. The three patients with former renal transplants were excluded from the PTA group in the analysis of measured GFR before and after pancreas transplantation.

Both recipient groups were given similar immunosuppressive therapy, including induction therapy with ATG (Thymoglobulin) and standard maintenance tacrolimus treatment (tacrolimus trough levels of 10–12 tapered to 6–10 µg/L by 8 weeks), mycophenolate mofetil

(MMF) 1 g twice daily and steroids (tapered to 10 mg/day by week 4 and 5 mg/day by week 26). One patient was given azathioprine instead of MMF due to mycophenolate intolerance.

Measured GFR and OGTT investigations were scheduled on the same day and performed in the same laboratory at the transplant center at 8 and 52 weeks after transplantation. The OGTT was performed after at least 8 h of fasting with oral administration of 75 g glucose in 200 mL of water. Patients were instructed to stay on a weight-maintaining diet for 3 days prior to testing and abstain from alcohol. Glucose, insulin and C-peptide were measured just prior to, and 30 and 120 min after, the glucose load. Measured GFR was performed by the 2-point iohexol serum clearance method, starting with normal plasma glucose after the OGTT. Extended laboratory tests and assessment of clinical parameters were performed in the same session. The insulinogenic index ($\text{Insulin}_{30} - \text{Insulin}_0 / \text{Glucose}_{30} - \text{glucose}_0$, IGI) (11), and area under the concentration vs time curve (AUC) for glucose, insulin and C-peptide, were calculated from the OGTT data. As C-peptide is affected by kidney function, the quotient of fasting C-peptide/fasting glucose $\times$ P-creatinine was also calculated (12).

Homeostasis model assessment of insulin resistance (HOMA2_{IR}) and beta cell function ($\text{HOMA2}_{\text{B}\%}$) were calculated according to the fasting glucose and plasma C-peptide levels by the Web-based HOMA 2 calculator (13). C-peptide was used in these calculations as it is less confounded than insulin with regards to the missing first pass effect of the liver in pancreas grafts with caval venous drainage (14). We also calculated the ratio $\text{IGI}/\text{HOMA2}_{\text{IR}}$ with the intention of adjusting insulin secretion to insulin resistance.

All patients had their pre-transplant work-up performed in local hospitals before they were referred to the national transplant center. All PTA candidates had measured GFR investigations performed locally with plasma clearance methods according to center praxis, mostly ^{51}Cr -EDTA, as part of the work-up. The pre-transplant measurements represent variables sampled while the patients were on the waiting lists for transplantation; BMI, HbA1c, CMV IgG, blood pressure measurements, medication lists and urine albumin/creatinine results were collected for all pancreas transplant candidates, in order to compare pre- and post-transplant levels in this study.

Data included in this quality study were retrieved from the transplantation database at our center and analyses were performed on de-identified data. All patients who are included in the database gave written consent for saving

their clinical data and to use them in research and quality assessment studies. According to national guidelines, there was consequently no need for ethics approval for this quality analyses, but the quality study was approved by the Norwegian Data Inspectorate.

Data collection and statistical analyses

This is a retrospective analysis of prospectively collected data. Data analysis was performed using SPSS (version 22; IBM, Armonk, NY, USA). Categorical outcomes are described using frequencies and proportions while continuous variables are described using mean $\pm$ s.d. Group comparisons were performed by a Student's *t*-test, chi-square test or Fishers' exact test when appropriate. *P* values were reported according to two-tailed analysis, and *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics of the two groups are presented in Table 1. It was a higher share of men in the SPK than in the PTA group (73 vs 51%) and the mean pre-transplant mGFR was, by selection, higher in the PTA group. The groups were otherwise comparable with regards to age, duration of diabetes, daily doses of insulin, HbA1c, BMI and degree of HLA mismatches at transplantation. Stable simplex retinopathy with no signs of proliferative changes was confirmed by ophthalmologic examination prior to wait listing. The 28 patients who did not perform the investigations at week 8 did not differ with regards to the patient characteristics listed in Table 1. The fourteen patients who performed the investigations at 8 weeks but not at 52 weeks had comparable OGTT results at 8 weeks as those repeating the investigation at week 52 (data not shown). Mean prednisolone doses and tacrolimus through concentrations declined, in accordance with the center protocol, from week 8 to week 52 for both SPK and PTA recipients (Table 2).

Simultaneous pancreas and kidney transplant (SPK) recipients

Among 30 included SPK recipients, 15 were CMV IgG negative pre transplant. Thirteen of the latter (87%), who were transplanted with grafts from CMV IgG-positive donors, received prophylactic treatment with 900 mg valganciclovir once daily for 6 months (doses adjusted to renal function).

Clinical Study	E Nordheim and others	A single-center study	179:4	254
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Table 1 Baseline characteristics of SPK and PTA recipients before transplantation.

	SPK (n=30)	PTA (n=37)
Age	42.4±6.5	41.7±9.9
Males (%)	22 (73%)	19 (51%)
Duration of diabetes (years)	30.6±6.4	26.6±10.5
Daily dose of insulin (IU)	39.5±13.1	49.9±22.3
HLA mismatch (%)		
1–2	1 (3%)	0
3–4	9 (30%)	17 (46%)
5–6	20 (67%)	20 (54%)
HbA1c (%)	8.5±1.5	8.9±1.5
HbA1c (mmol/mol)	69.6±16.7	73.7±16.4
BMI (kg/m ²)	23.5±3.1	25.8±3.5
Measured GFR (mL/min/1.73 m ²)	<30	94 ^a ±22

^aThree patients were excluded from the PTA group in the analysis of measured GFR due to prior kidney transplantation.

The mean blood pressure was 141±22/81±11 mmHg pre transplant, 134±21/78±12 mmHg at 8 weeks post transplant and 134±15/76±10 mmHg at 52 weeks post transplant. Eighty-three percent of SPK recipients were treated with antihypertensive medication pre transplant, while 34% were treated with antihypertensive medication at 8 weeks and 52 weeks post transplant, respectively.

The mean urine albumin/creatinine ratio was 326±256 mg/mmol pre transplant, 4.9±5.4 mg/mmol 8 weeks post transplant and 3.2±6.8 mg/mmol 52 weeks post transplant.

Six SPK recipients had rejection episodes in either organ. One recipient had simultaneous rejections in kidney and pancreas graft, one recipient had solitary kidney graft rejection and four patients had solitary pancreas graft rejection. Five of these patients developed rejection within the first 8 weeks post transplant.

Mean tacrolimus trough level was 9.6±2.2 µg/L at 8 weeks post transplant and 7.8±2.2 µg/L at 52 weeks post transplant. At 8 weeks post transplant, the protocol-based maintenance dose of prednisolone was 10 mg while the accumulated dose was 760 mg. At 52 weeks post transplant, protocol-based maintenance dose was 5 mg while the accumulated dose was 2625 mg.

Eight weeks after transplantation, BMI and HbA1c were significantly reduced when compared to status pre-transplant; BMI fell from 23.5±3.1 kg/m² to 22.7±2.4 kg/m² ($P=0.01$) and HbA1c from 69.6±16.7 to 36.8±8.2 mmol/mol (8.5±1.5 to 5.6±0.7%; $P<0.005$).

The changes from 8 weeks to 52 weeks are shown in Table 2. HbA1c was 36.8 and 36.4 mmol/mol (5.6 and 5.5%; $P=0.72$) at weeks 8 and 52 respectively. Mean fasting plasma glucose, C-peptide and the quotient of C-peptide

(glucose×creatinine) decreased significantly. The mean C-peptide levels at 120 min were also lower (Fig. 2). Finally AUC₁₂₀ C-peptide, HOMA2_{IR} and IGI/HOMA2_{IR} decreased from week 8 to week 52, whereas the other parameters of glucose metabolism did not change significantly.

Measured GFR did not change significantly between weeks 8 and 52 (Table 2).

There was no significant correlation between change in fasting c-peptide values from week 8 to week 52 post transplant and measured GFR at week 52 post transplantation (Pearson correlation: -0.28 ; $P=0.19$). A correlation was found between change in fasting c-peptide values between week 8 and week 52 post transplantation and level of increasing urine albumin/creatinine level at week 52 post transplantation (Pearson correlation: 0.38 ; $P=0.04$).

SPK recipients who were not treated with hypertensive medication at week 52 post transplant had no significant difference in change of fasting c-peptide values between week 8 and week 52 post transplantation, compared to the recipients who were treated with such medication (mean 404±484 pmol/L/440±395 pmol/L; $P=0.41$).

PTA recipients

Of the 37 included PTA recipients, 19 were CMV IgG negative pre transplant. Eleven of these recipients (58%) were transplanted with grafts from CMV IgG-positive donors and received prophylactic treatment with valganciclovir for 6 months.

Mean blood pressure was 127±12/77±10 mmHg pre transplant, 129±14/77±7 mmHg 8 weeks post transplant and 126±11/77±8 mmHg 52 weeks post transplant. Thirty-eight percent of the PTA recipients were treated with antihypertensive medication pre transplant, 18% at 8 weeks and 26% at 52 weeks post transplant.

The mean urine albumin/creatinine ratio was 21.7±69.0 mg/mmol pre transplant, 6.7±16.0 mg/mmol 8 weeks post transplant and 9.7±22.3 mg/mmol 52 weeks post transplant.

Sixteen PTA recipients had at least 1 rejection episode during the study period; 2 recipients had two rejection episodes while 14 recipients had one rejection episode during the first year post transplant. Fifteen of these recipients developed rejection within the first 8 weeks post transplant, while two recipients developed rejection between week 8 and week 52 post transplant.

Mean tacrolimus trough level was 9.4±2.4 µg/L at 8 weeks post transplant and 7.5±2.5 µg/L at 52 weeks

Table 2 Mean $\pm$ s.d. of clinical characteristics, metabolic parameters and immune suppressive therapy at weeks 8 and 52 post transplantation in patients successfully transplanted with simultaneous pancreas and kidney transplantation (SPK group) and PTA group.

	SPK group (n=30)			PTA group (n=37)		
	8 weeks post-tx	52 weeks post-tx	P-Value	8 weeks post-tx	52 weeks post-tx	P-Value
Fasting P-Glucose (mmol/L)	5.4 $\pm$ 0.7	5.1 $\pm$ 0.8	0.02	5.4 $\pm$ 0.6	5.2 $\pm$ 0.7	0.005
P-Glucose _{2h} (mmol/L)	6.9 $\pm$ 2.9	5.7 $\pm$ 2.2	0.07	6.5 $\pm$ 1.7	5.7 $\pm$ 1.2	0.03
Fasting P-Insulin (pmol/L)	187 $\pm$ 99	161 $\pm$ 79	0.08	195 $\pm$ 121	178 $\pm$ 139.9	0.02
P-Insulin _{2h} (pmol/L)	490 $\pm$ 316	435 $\pm$ 303	0.36	380 $\pm$ 211	361 $\pm$ 194	0.02
Fasting P-C-peptide (pmol/L)	1500 $\pm$ 573	1078 $\pm$ 357	<0.005	1210 $\pm$ 487	1021 $\pm$ 434	<0.005
P-C-peptide _{2h} (pmol/L)	3378 $\pm$ 1646	2650 $\pm$ 1189	0.02	2469 $\pm$ 831	2329 $\pm$ 820	<0.005
AUC ₁₂₀ glucose	949.2 $\pm$ 211.3	885.9 $\pm$ 193.3	0.14	920.4 $\pm$ 129.3	896.1 $\pm$ 121.5	0.009
AUC ₁₂₀ insulin	66412 $\pm$ 39147	65005 $\pm$ 34954	0.81	56318 $\pm$ 23756	55958 $\pm$ 24205	<0.005
AUC ₁₂₀ C-peptide	361620 $\pm$ 159666	294213 $\pm$ 100566	0.01	288064 $\pm$ 83950	264208 $\pm$ 93531	<0.005
IGI	167.9 $\pm$ 216.5	217.3 $\pm$ 183.6	0.23	199.5 $\pm$ 248.2	169.6 $\pm$ 196.1	0.67
HOMA2 _{B*}	196.6 $\pm$ 65.1	170.5 $\pm$ 48.4	0.05	165.5 $\pm$ 49.5	158.9 $\pm$ 57.9	<0.005
HOMA2 _{IR*}	3.5 $\pm$ 1.5	2.4 $\pm$ 0.8	<0.005	2.7 $\pm$ 1.1	2.3 $\pm$ 0.9	<0.005
IGI/HOMA2 _{IR*}	52.0 $\pm$ 64.9	100.5 $\pm$ 95.9	0.005	86.7 $\pm$ 120.8	79.2 $\pm$ 82.4	0.12
HbA1c (%)	5.6 $\pm$ 0.7	5.5 $\pm$ 0.6	0.72	5.6 $\pm$ 0.7	5.4 $\pm$ 0.5	0.01
HbA1c (mmol/mol)	36.8 $\pm$ 8.2	36.4 $\pm$ 6.9	0.72	37.9 $\pm$ 7.1	35.1 $\pm$ 5.1	0.01
Creatinine (μ mol/L)	110.3 $\pm$ 32.1	105.7 $\pm$ 30.5	0.40	95.8 $\pm$ 41.2	101.9 $\pm$ 35.8	<0.005
C-peptide/glucose $\times$ creatinine (pmol/mmol/L μ mol/L)	2.7 $\pm$ 1.3	2.1 $\pm$ 0.8	<0.005	2.6 $\pm$ 1.1	2.3 $\pm$ 0.8	<0.005
GFR measured (mL/min/1.73 m ²)	55 $\pm$ 15	60 $\pm$ 11	0.19	76 $\pm$ 19	77 $\pm$ 20	0.74 ^a
BMI (kg/m ²)	22.7 $\pm$ 2.4	24.2 $\pm$ 4.4	0.02	25.0 $\pm$ 3.0	25.4 $\pm$ 4.3	<0.005
Mean dose prednisolone (mg)	9.6 $\pm$ 2.9	5.2 $\pm$ 0.8	<0.005	9.3 $\pm$ 2.9	5.3 $\pm$ 0.9	0.68
Mean trough tacrolimus concentration (μ g/L)	9.6 $\pm$ 2.2	7.8 $\pm$ 2.2	0.02	9.4 $\pm$ 2.4	7.5 $\pm$ 2.5	0.16

^aThree patients were excluded from the PTA group in the analysis of measured GFR due to prior kidney transplantation.AUC₁₂₀, area under the curve calculated by the trapezoidal rule based on values obtained 0, 30 and 120 min during the oral glucose tolerance test; Glucose/Insulin/C-peptide_{2h}, 2h plasma value during oral glucose tolerance test; HOMA2_{B*}, homeostasis model assessment of beta cell function calculated from fasting values of glucose and C-peptide; HOMA2_{IR*}, homeostasis model assessment of insulin resistance calculated from fasting values of glucose and C-peptide; IGI, insulinogenic index (Insulin₃₀-Insulin₀/Glucose₃₀-Glucose₀).

Figure 2

OGTT results for blood glucose measured at 8 weeks and 52 weeks post transplant for SPK (A) and PTA recipients (B) and C-peptide measured at 8 weeks and 52 weeks post transplant for SPK (C) and PTA recipients (D) referred as mean $\pm$ S.E.M.

post transplant. At 8 weeks post transplant the protocol-based maintenance dose of prednisolone was 10mg while the accumulated dose was 760mg. At 52 weeks post transplant protocol-based maintenance dose was 5mg while the accumulated dose was 2625 mg.

Eight weeks after transplantation BMI and HbA1c were significantly reduced when compared to status pre-transplant; BMI was reduced from $25.8 \pm 3.5 \text{ kg/m}^2$ to $25.0 \pm 3.0 \text{ kg/m}^2$ ($P=0.006$) and HbA1c from 73.7 ± 16.4 to $37.9 \pm 7.1 \text{ mmol/mol}$ ($8.9 \pm 1.5\%$ to $5.6 \pm 0.7\%$; $P<0.005$).

The changes from 8 weeks to 52 weeks are shown in Table 2. HbA1c was further reduced from 37.9 to 35.1 mmol/mol (5.6 to 5.4%, $P=0.01$). Mean fasting plasma glucose, insulin, C-peptide and the quotient of C-peptide/(glucose $\times$ creatinine) decreased significantly. Mean glucose, insulin and C-peptide levels at 120 min also decreased significantly (Fig. 2). Finally AUC_{120} for glucose, insulin and C-peptide and also HOMA2_{IR} and HOMA2_{B} decreased from week 8 to week 52.

Measured GFR decreased from the time the patients were listed for transplantation until week eight after transplantation (94 ± 22 to $78 \pm 19 \text{ mL/min/1.73 m}^2$; $P<0.005$) while no change was observed from week 8 to week 52 (Table 2).

BMI increased from week 8 to week 52 after transplantation.

There was no significant correlation between change in fasting c-peptide values from week 8 to week 52 post-transplant and measured GFR at week 52 post transplantation (Pearson correlation coefficient:

-0.17 ; $P=0.35$). Furthermore, there was no significant correlation between change in fasting c-peptide values between week 8 and week 52 post transplantation and level of urine albumin/creatinine level at week 52 post transplantation (Pearson correlation: 0.03; $P=0.87$). PTA recipients who were not treated with hypertensive medication at week 52 post transplant, had no significant difference in change of fasting c-peptide values between week 8 and week 52 post transplantation, compared to the recipients who were treated with such medication (mean $234 \pm 327 \text{ pmol/L}$ / $164 \pm 272 \text{ pmol/L}$; $P=0.49$).

Discussion

Our main findings are that glucose control and mGFR are preserved 1 year after successful pancreas transplantation. Insulin secretion decreases in parallel with lower insulin resistance.

In contrast to most publications reporting on glucose metabolism after pancreas transplantation, our material consists of a majority of PTA recipients. In patients with functioning pancreas transplant grafts the mean levels of glucose and C-peptide were found significantly reduced after 1 year, but still within the normal range for both PTA and SPK recipients. Preserved glucose homeostasis after pancreas transplantation has been reported even 15 years after transplantation in selected patients (15). Dieterle *et al.* found a slight and continuous increase of fasting glucose within the normal range in their study of insulin-independent SPK recipients who were followed with OGTTs for over 10 years. Luzi *et al.* demonstrated that euglycaemic-hyperinsulinaemic clamp determined insulin sensitivity normalized in six SPK patients after 12 months in their study (16).

Insulin response in target cells is not only dependent on plasma insulin concentrations, but also on insulin sensitivity. State-of-the-art measurement of insulin sensitivity is performed with an euglycaemic-hyperinsulinaemic clamp technique (17), but the technique is not suitable for routine clinical use and was not available to us in the present study. Insulin resistance and beta-cell function have been estimated in large groups of patients from fasting glucose and insulin levels, e.g. with the homeostasis model assessment (HOMA) (18). HOMA calculations of beta cell function and insulin resistance ($\text{HOMA}_{\text{B}\%}$ and HOMA_{IR}) are validated for patients with various degrees of glucose intolerance, but less so for transplant recipients. As our pancreas transplant recipients drain insulin to the systemic and not to the

portal circulation, the liver and the periphery are exposed to similar levels of insulin.

In our patients, who did not have any need for glucose-lowering agents or insulin, the insulin secretion seems well preserved both 8 weeks and 1 year after transplantation. HOMA2_{IR} was lower 1 year post transplant for both recipient groups despite increase in BMI. Given the change in HOMA2_{IR} represents true improvement in insulin sensitivity, it is most likely caused by tapering of immunosuppressive agents in the same period.

Successful pancreas transplantation normalizes blood glucose, which could reduce the progression of diabetic nephropathy (19), but immunosuppression and other transplant-related factors may on the other hand affect renal function negatively. One year after pancreas transplantation, the renal function in both transplanted and native kidneys were well preserved in our patients. The five-year cumulative risk for end-stage renal disease in patients undergoing non-renal organ transplantation has been reported to be 10.9% after heart transplantation and 18.1% after liver transplantation, and treatment with calcineurin inhibitors, age and era of transplantation are among risk factors that could explain this (20). Reports on renal function after pancreas transplantation are mostly case series and with partly conflicting results. Decline in renal function 5 years after PTA was observed by Le Dinh (21). In fact, deterioration of renal function may be observed regardless of pre-transplant renal function (22). Others have reported that pre-transplant renal function may be of importance: PTA recipients with creatinine clearance below 70 mL/min/1.73 m² before transplantation had a significant risk of worsened renal function after transplantation in one study (23), while another report suggested that native renal function declined only in PTA recipients with pre-transplant GFR > 90 mL/min/1.73 m² possibly due to correction of hyperfiltration as a result of normalized glucose levels (24).

Our PTA patients had mGFRs ranging 35–134 mL/min/1.73 m² before transplantation, and only seven patients had mGFR < 70 mL/min/1.73 m². Our PTA recipients also showed a significant decline in mGFR from the time they were listed for transplantation until 8 weeks after transplantation during median waiting time 199 days (range 28–500). The decline in renal function after pancreas transplantation may support the findings by Buggi *et al.* (24).

Immunosuppressive therapy may affect both insulin secretion and sensitivity, as well as renal function

negatively after transplantation. Our maintenance immunosuppressive protocol included use of 5 mg prednisolone, and our center has previously reported that withdrawal of such a dose does not improve insulin sensitivity measured by a hyperinsulinemic–euglycemic clamp technique (25). Others have reported that tacrolimus and cyclosporine do not differ regarding their effects on glucose metabolism and insulin secretory capacity 3 years after SPK (26). In renal transplant recipients, however, insulin sensitivity has been found to be negatively correlated with trough levels of tacrolimus (27). Chatzizacharias *et al.* found that high tacrolimus trough levels at 6 months post transplant were the only independent risk factor for decline in renal function in PTA recipients over 2 years (28). All our patients were treated with tacrolimus at lower trough levels 1 year compared to 8 weeks after transplantation.

The strength of our study is the sample size, and that it is a national cohort and the longitudinal design. All included patients were transplanted at the national transplant center with the same surgical technique, treated according to the same immunosuppressive protocol and all underwent a standardized follow-up. Renal function was assessed using mGFR, which is more precise than estimated GFR by creatinine or cystatin C algorithms. The major limitations of our study are the fact that only 60% of all patients transplanted in the study time period were included in the analyses, as we excluded the patients who were not investigated with OGTTs twice. Unfortunately, we do not have follow-up data for changes in retinopathy or neuropathy (neither peripheral nor autonomous neuropathy). The restricted follow-up period of 1 year is also a limitation of the study.

Our findings are reassuring since they indicate that patients undergoing clinically successful pancreas transplantation maintain normal glucose homeostasis as measured by C-peptide indices and that kidney function is stable, at least during the first year after transplantation. Interpretation of our results must be done in light of the inclusion criteria of the study.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

E N, K I B and T J developed the study concept and design, performed the analysis and interpretation of data, drafted the manuscript, performed critical revision of the manuscript for important intellectual content and performed statistical analysis. A H, R H and A Å performed critical revision of the manuscript for important intellectual content.

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E N is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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