Endothelial function after pancreas transplantation—A single-center observational study

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Abstract

Background: Patients with diabetes mellitus treated with successful pancreas transplantation (PTX) normalize hyperglycemia, but are exposed to immunosuppressive drugs that may impair endothelial function. This study aimed to evaluate endothelial function in single PTX recipients.

Methods: Flow-mediated dilatation (FMD) in the brachial artery was measured by ultrasound 8 weeks after transplantation in single PTX (n = 27) and compared with healthy controls (n = 58), simultaneous pancreas and kidney recipients (n = 9), and kidney transplant recipients with (n = 41) and without (n = 95) diabetes mellitus. Adjustments for age, gender, blood pressure, and body mass index were included in a linear regression model. Changes in FMD from before to 1 year after transplantation were assessed in a subgroup of PTX recipients (n = 9).

Results: Flow-mediated dilatation% in PTX recipients was not inferior to healthy controls (8.7 ± 3.6 vs 7.7 ± 3.3, P = .06) and simultaneous pancreas and kidney recipients (6.7 ± 4.5, P = .24) in an adjusted model, and superior to kidney recipients with and without diabetes (3.0 ± 3.0 and 4.8 ± 3.3, respectively, both P < .005). FMD% improved significantly from eight weeks to one year after PTX, mean 7.9 ± 4.2% vs 11.8 ± 4.8% (N = 9; P = .03).

Conclusion: Flow-mediated dilatation is well preserved in patients undergoing pancreas transplantation and is not impaired when immunosuppressive drugs are introduced.

KEYWORDS

diabetes, endothelial function, immunosuppressive therapy, pancreas transplantation

1 | INTRODUCTION

The endothelium plays an important role in vessel diameter regulation, blood pressure, cell proliferation, inflammation, and blood clotting. Endothelial dysfunction may be an early sign of atherosclerotic disease and is associated with increased cardiovascular risk.[1] Diabetes mellitus can lead to endothelial dysfunction through hyperglycemia, but also impaired endothelial reparatory mechanisms have been suggested.[2,3] Patients with diabetes have an increased risk for cardiovascular disease (CVD), but this risk may be lowered if glycemia is maintained close to normal over many years, and more so if tight glucose control is initiated early after diagnosis.[4]

The flow-mediated dilatation (FMD) in the brachial artery is a noninvasive, validated measure of endothelial dysfunction. In this

test, high-resolution ultrasound is used to quantify the endothelium-dependent vasodilation occurring during hyperemia after a brief period of blood stasis.[5] This vasodilatation mainly depends on the bioavailability of nitrogen monoxide (NO) liberated by endothelial cells when exposed to an increased blood flow.[6] NO has numerous anti-atherosclerotic properties, including inhibition of platelet and leukocyte adhesion and smooth muscle proliferation.[7-9] Impaired FMD has been associated with CVD in the general population.[10]

Pancreas transplantation is a therapeutic option when type 1 diabetes cannot be controlled by exogenous insulin treatment. When successfully performed, glucose levels are normalized without any need for glucose-lowering therapy, and protection from both renal and neural complications has been described.[11,12] Whether pancreas transplantation has an implication of established macrovascular disease is not clear.

Any beneficial effect on endothelial function by normalizing blood glucose levels after pancreas transplantation could theoretically be counteracted by side effects of immunosuppressive drugs. Glucocorticoids and calcineurin inhibitors are part of the immunosuppressive treatment and are reported to have potential negative effects on endothelial function.[13-15] Furthermore, previous studies on this topic have focused of patients with renal failure undergoing simultaneous pancreas and kidney transplantation (SPK) [16,17].

The present study is the first of its kind to evaluate FMD in single–pancreas transplant patients, often referred to as pancreas transplantation–alone (PTA) recipients. It was conducted in order to improve our understanding of endothelial function in pancreas transplant recipients.

2 | MATERIALS AND METHODS

Two separate analyses were conducted. First, cross-sectional FMD results from PTA recipients were compared to corresponding results in healthy controls, SPK recipients, and kidney transplant (KTX) recipients with and without diabetes mellitus in a linear regression model. All FMD assessments in PTA, SPK, and KTX recipients were conducted eight weeks after transplantation. Second, available FMD results for PTA recipients who had assessments before transplantation and 8 and 52 weeks after transplantation were analyzed for changes in FMD following transplantation using paired-samples statistics.

2.1 | Study population

All study participants gave their informed written consent for study participation, and the study was approved by the Regional Ethics Committee.

Twenty-seven Norwegian patients who underwent PTA at our hospital between December 2013 and October 2015 were evaluated with flow-mediated dilatation test 8 weeks after transplantation as part of the DIAMANT study (ClinicalTrials.gov: NCT02066350). All PTA 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, illustrated in Figure 1. Nine out of the PTA recipients had three FMD assessments: before transplantation, 8 weeks, and one year after transplantation. All PTA recipients were given the same immunosuppressive therapy, which included induction therapy with antithymoglobulin (Thymoglobulin ®) and standard maintenance tacrolimus treatment (tacrolimus trough level target of 10-12 tapered to 6-10 µg/L by 8 weeks), mycophenolate mofetil (MMF) 1 g twice daily, and steroids (20 mg, tapered to 10 mg/day by week 4 and 5 mg/day by week 26). Candidates for PTA were patients with type 1 diabetes mellitus (DM) with "brittle diabetes" phenotype. Repeated episodes of severe hypoglycemia with impaired awareness for hypoglycemic symptoms were the main indication for PTA in 16 patients and repeated episodes of severe hyperglycemia in 6 patients, while unpredictable fluctuating levels of blood glucose were the main indication in 5 patients. Unawareness for hypoglycemic symptoms was present in 16 out of the patients. In our transplant protocol, PTA is restricted to patients with measured glomerular filtration rate (GFR) >30 mL/min/1.73m^2.

Healthy controls were randomly selected from the Norwegian population register. Responders with a history of diabetes mellitus (DM), hypertension, or reduced renal function were excluded.[18] Included persons underwent clinical examination and blood test sampling in addition to FMD assessment.

A cohort of patients with type 1 DM, who underwent SPK in the same transplant era as the PTA recipients, also had FMD assessment

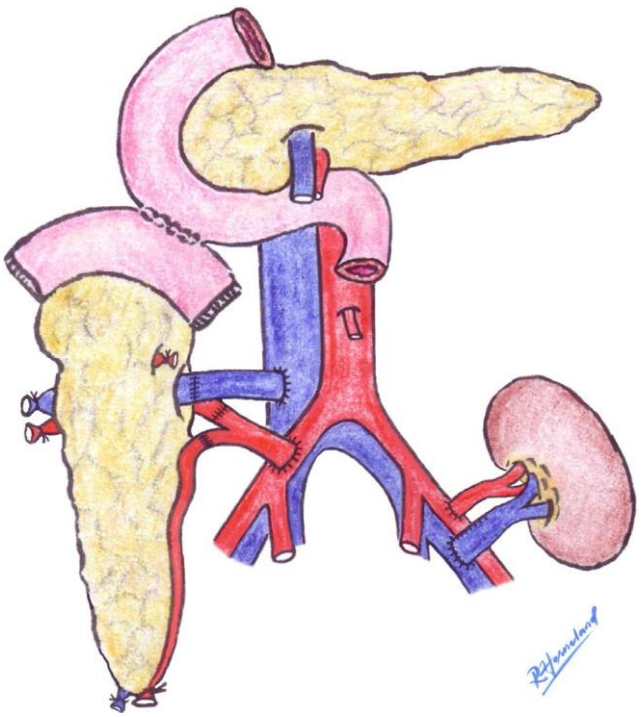

FIGURE 1 Vascular and enteric anastomoses utilized in our center for pancreas and kidney transplantation illustrated by Rune Horneland

8 weeks after transplantation. The immunosuppression protocol was similar to PTA recipients.

Single–kidney transplant (KTX, n = 136) was studied from the same era of kidney recipients as the SPK recipients. Out of the KTX recipients, 6 patients had pretransplant type 1 DM, 24 patients had pretransplant type 2 DM while 11 recipients developed diabetes mellitus after transplantation. In this study, all KTX cases with diabetes mellitus were pooled with regards to the current analyses.

KTX recipients had basiliximab induction and tacrolimus-based maintenance immunosuppressive therapy with lower intensity than the pancreas transplant recipients: tacrolimus trough target (3-7 μg/L) and MMF dose 750mg twice a day.

2.2 | Flow-mediated dilatation assessment

Flow-mediated dilatation measurements were performed by two dedicated clinicians (DOD/TH) as described previously.[19] In short, the brachial artery was visualized 5 cm proximal to the antecubital fossa with a 12-MHz linear array ultrasound probe (Zonare z.one; ZONARE Medical Systems) and diameters measured with the caliper tool. Baseline diameter was measured before 5 minutes of forearm blood flow occlusion using a sphygmomanometer cuff inflated to approximately 200 mm Hg. After cuff release, reactive hyperemia occurs and the maximal diameter during the following 90 seconds was used to calculate FMD. FMD% is the percentage increase in diameter from baseline, calculated as FMD%=100*(maximal diameter-baseline diameter)/baselinediameter.

2.3 | Statistical analyses

Baseline data are presented as mean ± SD or proportions, as appropriate.

To be able to adjust for all the intergroup differences listed in Table 1, cross-sectional FMD results from PTA recipients were compared to corresponding results in healthy controls, SPK recipients, and KTX recipients with and without diabetes mellitus in multiple linear regression models. In this way, we were able to identify the

TABLE 1 Clinical characteristics at week 8 after transplantation in healthy controls, pancreas transplantation–alone recipients, simultaneous pancreas and kidney transplantation recipients, and kidney transplantation–alone recipients without and with diabetes mellitus referred as mean ± SD

	Healthy controls n = 58	PTA n = 27	SPK n = 9	KTX with DM[a] n = 41	KTX without DM n = 95
Age, y	37.6 ± 3.9	40.9 ± 8.2	39.5 ± 7.0	59.6 ± 10.3	54.0 ± 13.1
Sex, percentage men	19	52	44	68	67
BMI, kg/m^2	25.8 ± 4.6	25.5 ± 3.8	23.3 ± 4.5	26.1 ± 4.5	24.4 ± 3.6
Systolic blood pressure, mm Hg	115 ± 12	125 ± 20	138 ± 20	154 ± 27	141 ± 19
Diastolic blood pressure, mm Hg	75 ± 8	78 ± 10	80 ± 15	78 ± 11	81 ± 10
eGFR, ckd-epi		76 ± 23	82 ± 25	57 ± 22	59 ± 19
Fasting Glucose, mmol/L	5.1 ± 0.5	5.4 ± 0.6	4.9 ± 0.6	6.4 ± 1.3	5.1 ± 0.7
HbA1c, mmol/mol	36 ± 3	40 ± 6	36 ± 7	54 ± 14	39 ± 5
HbA1c, percentage	5.4 ± 0.3	5.8 ± 0.6	5.4 ± 0.6	7.0 ± 1.3	5.7 ± 0.5
Current smokers, percentage	31	7	44	29	14
Previous smoker, percentage	28	41	33	29	34
LDL, mmol/L	3.0 ± 0.9	3.3 ± 0.8	2.8 ± 0.9	3.7 ± 1.3	3.6 ± 1.0
HDL, mmol/L	1.6 ± 0.4	1.6 ± 0.4	1.9 ± 0.5	1.5 ± 0.6	1.6 ± 0.5
Dose prednisolone, mg		11.2 ± 4.7	10.0 ± 3.9	10.8 ± 4.2	9.8 ± 3.8
Trough tacrolimus, μg/L		10.2 ± 2.5	7.9 ± 1.5	6.4 ± 1.7	6.3 ± 1.8
Dose mycophenolate mofetil, mg		1963 ± 192	1929 ± 189	1526 ± 283	1468 ± 230
Duration of diabetes mellitus, years		25.9 ± 10.7	27.1 ± 10.9	17.0 ± 11.0	
Duration of pretransplant dialysis, months			9.2 ± 9.1	48.8 ± 81.2	43.7 ± 84.99
FMD,%	7.7 ± 3.3	8.7 ± 3.6	6.7 ± 4.5	3.0 ± 3.0	4.8 ± 3.3

Abbreviations: BMI, body mass index; DM, diabetes mellitus; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTDM, post-transplant diabetes mellitus.

[a]This group includes PTDM, DM1, and DM2 patients.

explanatory variables that contributed to the outcome variable. We chose the stepwise procedure in the SPPS software for the entering of explanatory variables into the multiple regression models. For multiple regression models, the equation that best explains the regression line is $f(x) = a + b_1x_1 + b_2x_2 + b_3x_3 + \cdots b_nx_n$ where "a" is the intercept and each fragment of the formula is the weight of each explanatory variable.

In the longitudinal analysis, the longitudinal results were compared by Student's *t* test.

SPSS version 25 (IBM) was used for the analyses, and two-sided *P*-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients

Clinical characteristics of PTA recipients, healthy controls, and simultaneous pancreas and single–kidney transplant recipients with and without diabetes mellitus are presented in Table 1. Healthy controls had lower blood pressure and comprised of a higher proportion of females than the other groups. Single–kidney transplant (KTX) recipients were older, had higher blood pressure, and included more males. Mean blood pressure was highest in kidney transplant recipients with diabetes mellitus. KTX patients with diabetes had the longest mean duration of renal replacement therapy.

3.2 | Flow-mediated dilatation

Flow-mediated dilatation% in arteria brachialis for healthy controls and the transplant recipients group at 8 weeks after transplantation is presented as boxplots in Figure 2. In crude analysis, the mean FMD% in PTA recipients (8.7 ± 3.6) was not inferior to healthy controls (7.7 ± 3.3, *P* = .24) nor SPK recipients (6.7 ± 4.5, *P* = .13), whereas kidney recipients had inferior FMD% to PTA recipients: FMD% of 3.0 ± 3.0 in kidney recipients with diabetes and 4.8 ± 3.3 in kidney recipients without diabetes (both *P* < .005).

Endothelial function differed by gender and age. Men had lower mean FMD% than women (*P* = .04) and mean FMD% decreased by age (*P* = .04). In multivariable models demonstrated in Table 2, mean FMD% for PTA recipients was not confirmed significantly different from healthy controls. Kidney recipients with or without diabetes had significantly lower FMD% than healthy controls (both *P* < .004). SPK recipients had FMD% numerically in between PTA and KTX, though groupwise comparisons did not show statistical significant differences. We found no independent associations with FMD% in our analyses for the following: systolic blood pressure numbers, diastolic blood pressure numbers, plasma low-density lipoprotein (LDL), plasma high-density lipoprotein (HDL), current smoking status, previous smoking status, fasting glucose levels, renal function, duration of pretransplant dialysis, dose of prednisolone, trough level of tacrolimus, and dose of mycophenolate mofetil.

In a separate analysis of the kidney transplant recipients, we found that the patients with diabetes had significantly lower FMD% than the patients without diabetes (*P* = .03), in a model adjusted for age and gender. We found that FMD% among kidney transplant recipients was negatively associated with time in renal replacement therapy pretransplant.

3.3 | Repeated FMD assessments of pancreas transplant–alone recipients

The results of repeated FMD assessments (N = 9) before transplantation and 8 weeks and 52 weeks after transplantation are illustrated in Figure 3. Mean FMD% was 9.5 ± 5.8 before transplantation, 7.9 ± 4.2 8 weeks after transplantation, and 11.8 ± 4.8 fifty-two weeks after transplantation. FMD% did not change significantly from before to 8 weeks after transplantation (*P* = .34), while there

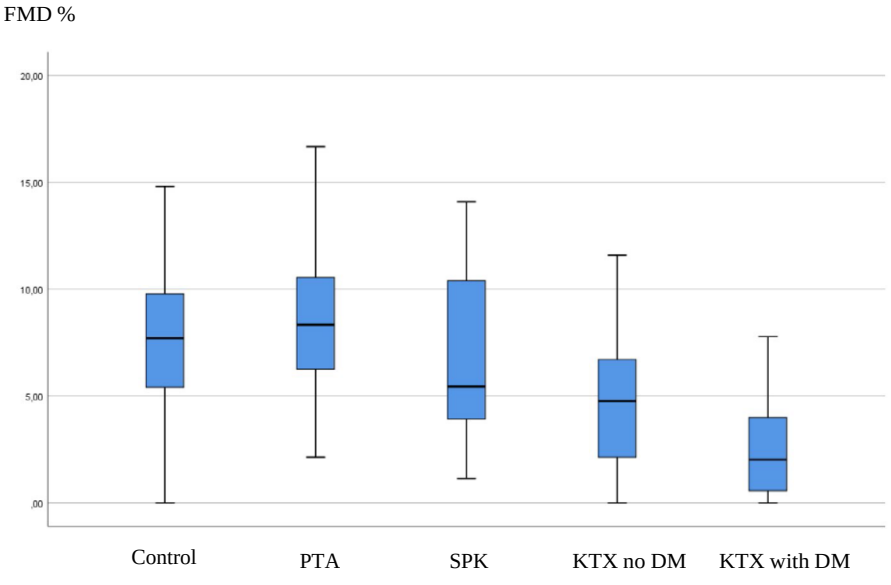

FIGURE 2 Flow-mediated dilatation% results for pancreas transplantation–alone recipients, healthy controls, simultaneous pancreas and kidney transplantation recipients, and kidney transplantation–alone recipients without and with diabetes mellitus (boxplots). DM, diabetes mellitus; FMD%, Flow- mediated dilatation: percentage change during test; KTX, kidney transplant recipients; PTA, pancreas transplant alone recipients; SPK, simultaneous pancreas and kidney transplant recipients

TABLE 2 FMD results from PTA recipients compared to corresponding results in healthy controls, SPK recipients, and KTX recipients with and without diabetes mellitus in multiple linear regression models

	Standardized coefficients Beta	*P*-value
FMD %		
PTA	Reference	Reference
Controls	−0.10	.24
SPK	−0.10	.13
KTX without DM	−0.50	<.005
KTX with DM	−0.56	<.005
FMD %		
PTA	Reference	Reference
Age, y	−0.28	<.005
Male, rate	−0.16	.01
Controls	−0.18	.04
SPK	−0.11	.08
KTX without DM	−0.34	<.005
KTX with DM	−0.40	<.005
FMD %		
PTA	Reference	Reference
Age, y	−0.20	.04
Male, rate	−0.17	.04
Systolic blood pressure, mm Hg	−0.02	.88
Diastolic blood pressure, mm Hg	0.12	.15
BMI, kg/m^2	−0.03	.64
HbA1c, %	−0.04	.69
Controls	−0.18	.06
SPK	−0.08	.24
KTX without DM	−0.45	<.005
KTX with DM	−0.42	<.005

Abbreviations: DM, diabetes mellitus; FMD%, flow-mediated dilatation: percentage increase during test; KTX, kidney transplant recipients; SPK, simultaneous pancreas and kidney transplant recipients.

was a significant increase from eight weeks to one year after transplantation ($P = .03$).

4 | DISCUSSION

Our main finding was that pancreas transplant–alone recipients had endothelial function, as measured by FMD, comparable to healthy controls eight weeks after transplantation despite high doses of immunosuppressive drugs. These results seemed sustained also one year after transplantation. This is to the best of our knowledge the first report on endothelial function in PTA recipients.

Before they received a pancreas transplant, our PTA candidates had mean diabetes duration of 26 years. Poorly controlled diabetes often leads to complications such as endothelial dysfunction and atherosclerosis[2,20] but preserved endothelial function in patients with well-established diabetes has also been reported.[21] In that particular study, endothelial function measured by FMD was not inferior in type 1 diabetes patients with long diabetes duration as compared to nondiabetic control subjects. These patients, however, were reported to have good long-term glycemic control, in contrast to our PTA recipients who had a mean pretransplant HbA_1c 85 ± 16 mmol/mol (8.9 ± 1.5%). Most of our PTA recipients had failed to achieve glucose targets as recommended with insulin therapy, and many of the candidates with a history of hypoglycemia unawareness often kept their glucose levels high before transplantation in order to prevent hypoglycemic episodes.

There are some reports on endothelial function after simultaneous pancreas and kidney transplantation, but these patients differ from our PTA recipients as they have a history of renal failure. It seems beneficial for patients with type 1 diabetes and end-stage renal disease, to be transplanted with SPK rather than kidney transplantation alone (KA). Two publications argue that endothelial function measured by FMD is better in SPK than KA recipients.[16,17] SPK recipients are also reported to have improved cardiovascular risk profile,[22] reduced incidence of myocardial infarction, stroke, and amputations,[23] and even better survival[24] than KA recipients.

Chronic kidney disease (CKD) patients have impaired FMD,[25] and we also found that kidney transplant recipients had inferior FMD results compared to the healthy controls. Whether this impairment in CKD patients is potentiated in patients with concurrent diabetes mellitus is not clear. In one study, FMD was not inferior in CKD patients with diabetes mellitus (n = 37) compared to CKD patients without diabetes.[26] We found that our kidney transplant recipients with diabetes had significantly lower FMD than our kidney transplant recipients without diabetes. The grade of reduced kidney function might contribute to this diversity as our kidney transplant recipients with and without diabetes had eGFR 57 and 59 mL/min/1.73m^2 while the CKD patients had 24 and 28 mL/min/1.73 m^2, respectively. In our study, the kidney transplant recipients with diabetes also had the longest duration of dialysis pretransplant.

It could be argued that use of immunosuppressant drugs itself would affect endothelial function, and there are a few clinical studies that report altered FMD measurement due to immunosuppressive therapy. Two minor studies found that repeated administration of glucocorticoids in nontransplanted populations was associated with endothelial dysfunction.[27,28] Morris reported that kidney transplant recipients had better endothelial function when treated with azathioprine compared to cyclosporine—despite longer total time in renal replacement therapy before transplantation.[15] Another study found no difference in FMD between kidney transplant recipients immunosuppressed with cyclosporine A and tacrolimus.[14] Cyclosporine A withdrawal was not found to affect FMD results in kidney transplant recipients six months after the drug was stopped.[29] Sirolimus might be associated with better FMD results in kidney transplant recipients

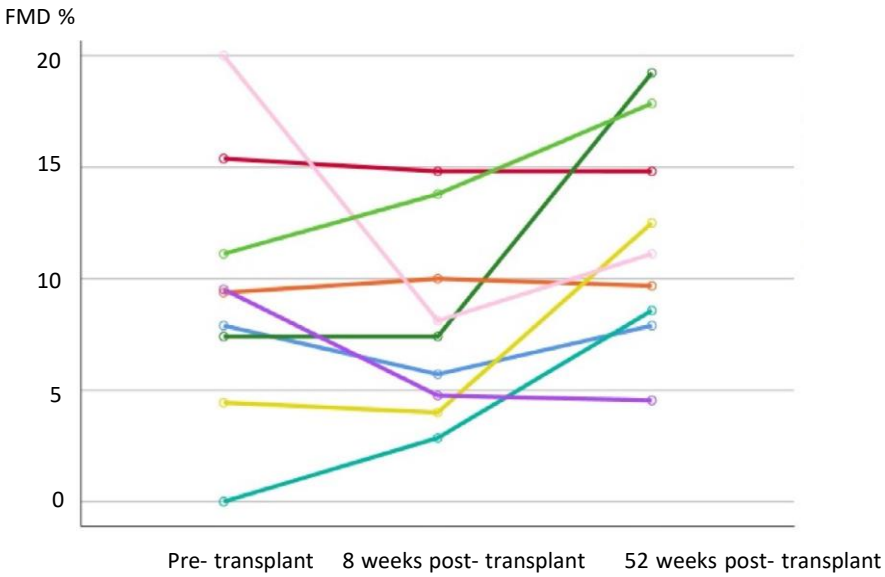

FIGURE 3 Flow-mediated dilatation% results at baseline before transplantation and at 8 and 52 wk after pancreas transplantation alone. FMD%, Flow-mediated dilatation: percentage change during test

than cyclosporine A.[30] In addition, in a recent study by Yiannoullou an increased risk for major adverse cardiovascular events was found in their Manchester cohort of SPK recipients immunosuppressed by prednisolone.[13] As our PTA recipients had superior FMD results to the kidney transplant recipients, despite treated with more intense immunosuppressive therapy, it is reasonable to assume that kidney function has more impact on FMD results than immunosuppression. There are no reports describing that various induction agents affect endothelial function differently that we are aware of, but as different induction is given to KTX and PTA recipients, this might be a confounder in this analysis.

The strength of this study is the novelty of FMD assessments in pancreas transplant–alone recipients. The numbers of patients in this study are limited, which is a reflection of the restricted number of patients treated with this modality. The restricted follow-up period of 1 year is another limitation of the study. Interpretation of our results must be done in light of the inclusion criteria of the study.

Our PTA recipients had no inferior FMD results at one year after transplantation compared to the results prior to transplantation, which indicate that FMD is preserved even with the possible negative effects from immunosuppressive drugs. Our findings are reassuring since they indicate that patients undergoing pancreas transplantation maintain normal and stable endothelial function, at least during the first year after transplantation.

ACKNOWLEDG EMENTS

EN 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.

CONFLICT OF INTERESTS

No conflict of interest relevant to this work for any of the authors.

AUTHOR CONTRIBUTIONS

EN, KB, and TGJ: Developed the study concept and design; EN and DOD: Performed the analysis, interpreted the data, and performed statistical analysis; EN and TGJ: Drafted the manuscript; and EN, DOD, TH, KIB, AÅ, AH, RH, and TGJ: Performed the critical revision of the manuscript for important intellectual content.

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How to cite this article: Nordheim E, Dahle DO, Halden T, et al. Endothelial function after pancreas transplantation—A single-center observational study. *Clin Transplant*. 2020;34:e13815. https://doi.org/10.1111/ctr.13815