RESEARCH

Patient selection for islet or solid organ pancreas transplantation: experiences from a multidisciplinary outpatient-clinic approach

Espen Nordheim[1,2], **Jørn Petter Lindahl**[1], **Rasmus Kirkeskov Carlsen**[1], **Anders Åsberg**[1,3], **Kåre Inge Birkeland**[1,2], **Rune Horneland**[4], **Birgitte Boye**[5,6], **Hanne Scholz**[4,7] and **Trond Geir Jenssen**[1,2,8]

[1]Department of Transplantation Medicine, Section of Nephrology, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[2]Faculty of Medicine, University of Oslo, Oslo, Norway
[3]Department of Pharmacy, University of Oslo, Oslo, Norway
[4]Department of Transplantation Medicine, Section of Transplantation Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[5]Psychosomatic and CL Psychiatry, Division of Mental Health and Addiction, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[6]Department of Behavioural Medicine, University of Oslo, Oslo, Norway
[7]Centre of Excellence-HTH, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway
[8]Metabolic and Renal Research Group, Faculty of Health Sciences, UiT-The Arctic University of Norway, Tromsø, Norway

Correspondence should be addressed to E Nordheim: b23697@ous-hf.no

Abstract

Objective: β-cell replacement therapy (βCRT), including pancreas transplantation alone (PTA) and islet transplantation (ITX), is a treatment option for selected type 1 diabetes patients. All potential candidates for βCRT in Norway are referred to one national transplant centre for evaluation before any pre-transplant workup is started. This evaluation was performed by a transplant nephrologist alone prior to 2015 and by a multidisciplinary team (MDT) from 2015. We have reviewed the allocation of patients to treatment modality and the 1-year clinical outcome for the patients after transplantation.
Research design and methods: Medical charts of all patients evaluated for βCRT between 2010 and 2020 in Norway were retrospectively analysed and the outcome of patients receiving βCRT were studied.
Results: One hundred and forty-four patients were assessed for βCRT eligibility between 2010 and 2020. After MDT evaluation was introduced for βCRT eligibility in 2015, the percentage of referred patients accepted for the transplant waiting list fell from 84% to 40% ($P < 0.005$). One year after transplantation, 73% of the PTA and none of the ITX patients were independent of exogenous insulin, 8% of the PTA and 90% of the ITX patients had partial graft function while 19% of the PTA and 10% of the ITX patients suffered from graft loss.
Conclusion: The acceptance rate for βCRT was significantly reduced during a 10-year observation period and 81% of the PTA and 90% of the ITX patients had partial or normal graft function 1 year post-transplant.

Key Words
- diabetes
- metabolism

Endocrine Connections (2021) **10**, 230–239

Introduction

Transplantation has become an established treatment option for selected patients with type 1 diabetes in many centres. Simultaneous pancreas and kidney (SPK) transplantation was offered to the first patient in history in Minnesota in 1966 (1) and is still the preferred treatment for end-stage renal disease in patients with type 1 diabetes. For patients with type 1 diabetes and preserved renal function, transplantation with single pancreas

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

(pancreas transplantation alone; PTA) or pancreatic islets (islet transplantation alone; ITX) are both treatment alternatives when conventional therapy fails.

In Norway, pancreas transplantation has been a treatment option performed mainly as SPK since 1983, while PTA has been performed only on a low scale before 2012 (2). Our centre started ITX in 2001, initially as part of a research programme before it was implemented as clinical treatment from 2009 (3). PTA and ITX are now considered as supplementary treatment modalities in the Norwegian programme for beta-cell replacement therapy (βCRT) for patients who are not in need of a simultaneous kidney graft. The surgical technique for pancreas transplantation was altered in our centre in 2012, utilizing duodeno–duodenal anastomosis for enteric drainage (4). This technique made it possible to perform endoscopic biopsies from the transplanted pancreas as well as the donor duodenal segment for rejection surveillance and elicited PTAs on a larger scale. Initial outcome reports with this technique have been published (5, 6, 7). The estimated number of people living with type 1 diabetes in Norway is 28,000 in a population of 5.4 million. A mean of 5.2 pancreas grafts have been transplanted per million each year since 2012 in Norway and 48% of these transplantations have been PTAs (8). The rate of ITXs has been quite stable, with a mean of 1.1 transplantations per million annually after 2009.

All patients who are considered candidates for βCRT in Norway are referred to our national centre for evaluation of transplant eligibility before any workup is initiated. The present study summarizes our experience with βCRT before (2010–2014) and after (2015–2019), the latter period introducing an organized multidisciplinary approach for allocation of referred patients. We also present 1-year clinical outcome data during the last 10 years.

Research design and methods

This is a single-centre, observational study approved by the hospital Data Protection Officer.

Selection criteria for beta-cell replacement therapy in Norway

Eligible candidates for βCRT were patients who had failed to achieve acceptable blood glucose control and quality of life with conventional therapy and technical aids available for the treatment of type 1 diabetes. Patients with different phenotypes of diabetes have been accepted, the major categories being patients with persistent hyperglycaemia (HbA1c > 10% (>86 mmol/mol)), patients with recurring episodes of hypoglycaemia or with fluctuating or unpredictable blood glucose levels, particularly combined with impaired awareness of hypoglycaemia. Patients with high HbA1c requiring ≥ 0.5 units/kg/day of insulin were primarily considered for PTA, while patients with impaired awareness for hypoglycaemia requiring < 0.5 units/kg/day were primarily considered for ITX (Fig. 1).

Organization

According to national guidelines, care for patients with type 1 diabetes in Norway is provided by their local or regional hospital. All solid organ transplant activity is performed at the national transplant centre located at Oslo University Hospital – Rikshospitalet while workup prior to wait-listing is performed at the local hospitals. Potential candidates for βCRT are referred to the transplant centre outpatient clinic for evaluation, before any pre-transplant workup is started, and all referred patients are offered an evaluation.

The main purposes of the transplant centre evaluation of potential βCRT candidates have been: (1) to update the patient on all available treatment modalities including updated information about modern insulin treatment with insulin pumps and hybrid closed-loop systems, (2) potentials risks and side-effects of the different transplantation options, (3) to search for any condition that might be a contraindication to transplantation, and (4) to help the patient reach an informed decision on which treatment modality he or she would prefer. When the patient is found eligible and is motivated for transplantation, all pre-transplant workup is initiated and the local hospital refers the patient back to the transplant centre when the workup is completed. The transplant centre lists the patient for transplantation if the workup is approved.

To build and maintain close cooperation around the patient, the transplant team regularly invite referring centres to meetings with lectures and discussions about procedures and cases.

Before 2015, the transplant centre's primary evaluation of potential βCRT candidates was performed by one single transplant nephrologist with special interest for diabetes. From 2015 and onwards this evaluation has been done by a multidisciplinary team (MDT).

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

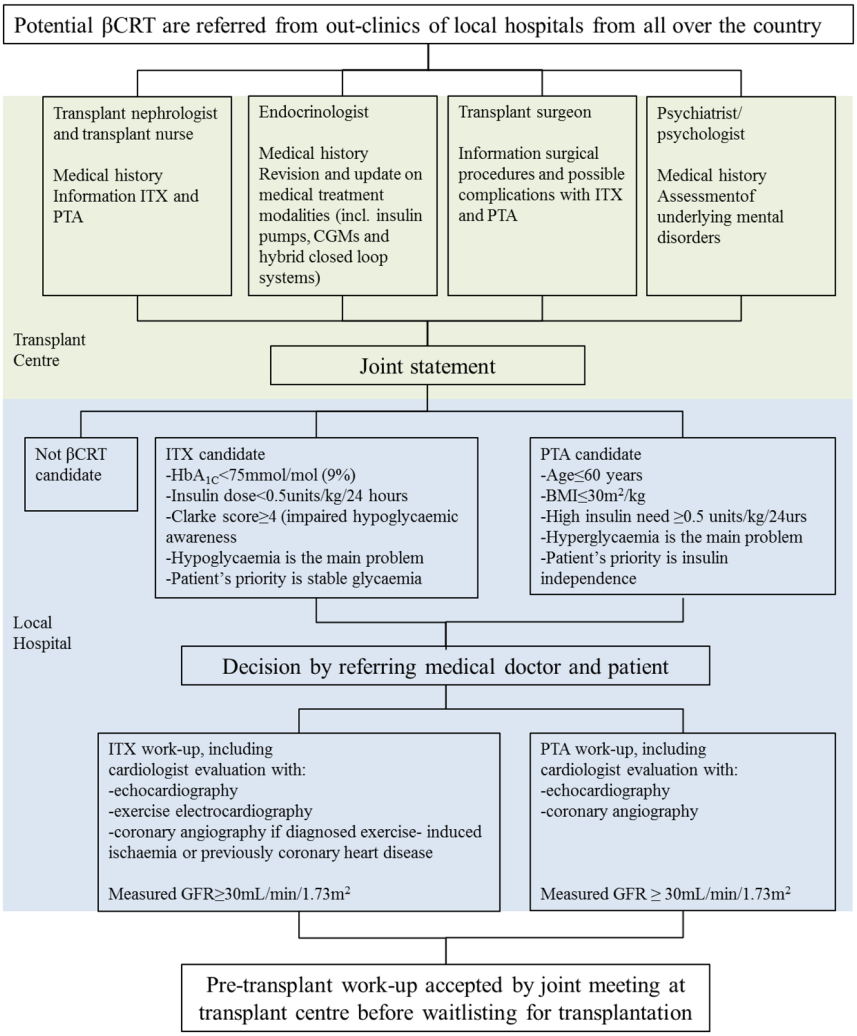

Figure 1
Decision chart for our multidisciplinary team evaluation of βCRT candidates.

Multidisciplinary team evaluation

The multidisciplinary team consists of an endocrinologist with expertise in type 1 diabetes, a transplant surgeon, a psychiatrist/psychologist with experience in evaluation of solid organ transplant candidates and a transplant nephrologist with expertise in diabetes.

Endocrinologist evaluation

The endocrinologist evaluation includes analysing the efforts which previously have been done for the patients, in order to optimize glucose-lowering therapy. For most included cases, we consider it mandatory that all modern aspects of type 1 diabetes treatment have been tried, before transplantation is a treatment option. This includes multiple injection regimes, continuous glucose monitors and insulin pumps including modern hybrid closed-loop systems. After hybrid closed-loop systems became available in Norway, most candidates considered for βCRT have been offered access to this technology before transplantation was considered. We assess the patients for impaired awareness of hypoglycaemia with Gold and Clarke scores (9, 10). Patients with low HbA1c-levels, who suffer from unawareness for hypoglycaemia or recurrent episodes of severe hypoglycaemia, are recommended to elevate HbA1c to at least 7.5% (58 mmol/mol) for at least 3 months before they are re-evaluated.

Surgical evaluation

The surgical evaluation includes a medical history with focus on previous surgery and relevant morbidity. The patients are informed about the transplant options including perioperative and post-operative aspects and the risks and complications of the surgical procedures.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

Psychiatric evaluation

The psychiatric evaluation consists of three parts to assess transplant eligibility and psychiatric contraindications. The first part is the relevant medical history while the second part is semi-structured psychiatric interviews. The third part is psychometric self-report schemes. Several scoring tool are used during the evaluation, including Mini neuropsychiatric interview (11), Montgomery-Åsberg depression rating scale (12), Stanford Integrated Psychosocial Assessment for Transplantation (13) and psychometric instruments to assess personality, burden of disease, and quality of life (14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25).

Nephrologist evaluation

The nephrologist coordinates the MDT and evaluates the patients with a thorough medical history focused on the patient's expectation and motivation for transplantation. The patient is informed about the transplant options, actual outcomes at our centre, potential side-effects of immunosuppressive drugs and post-transplant follow up.

Evaluation and differentiation of βCRT candidates

Figure 1 refers to the current decision chart for the evaluation and differentiation of βCRT candidates. βCRT candidates need to have a measured glomerular filtration rate (mGFR) at or above 30 mL/min/1.73 m^2 due to the known nephrotoxic effects of calcineurin-inhibiting treatment given after transplantation. Patients with GFR less than 30 mL/min/1.73 m^2 are considered for future simultaneous pancreas and kidney transplantation or pancreas after kidney transplantation. This treatment modality is offered when GFR runs below 20 mL/min/1.73 m^2. ITX has, throughout the study period, been presented to the patients as a treatment option which can prevent hypoglycaemic episodes and improve hypoglycaemic unawareness, but which does not ensure independence from exogenous insulin. For ITX candidates HbA_{1c} should not exceed 75 mmol/mol (9%) and exogenous insulin dose should not exceed 0.5 units/kg/24 h. Patients who want independence from exogenous insulin are recommended PTA if they are otherwise candidates for βCRT and tolerate the risks of the surgical procedure. BMI above 30 kg/m^2 and age above 60 years are both considered as contraindications for PTA at our centre. Cardiovascular assessment is a central part of the pre-transplant work up and the requirements are stricter for PTA than for ITX (Fig. 1). PTA candidates need a cardiologist evaluation with echocardiography and coronary angiography in addition to CT scan and MRI of aorta and the pelvic arteries.

Study population selection

In this study, we included all patients who were referred to the transplant centre for evaluation for first-time βCRT between January 2010 and January 2020. Patients previously transplanted were excluded. One hundred and forty-four patients met the inclusion criteria and 92 out of these were wait-listed for transplantation. Eighty-six patients were transplanted at the end of December 2019; 74 with PTA and 12 with ITX. The 12 included ITX patients received in total 25 ITX procedures; 2 patients received 1 ITX, 7 patients received 2 ITXs and 3 patients received 3 ITXs.

During the study period, in total 105 PTAs and 61 ITXs were performed in our centre. Out of the 105 PTAs, we included 74 PTAs in this study and excluded 31 cases due to pancreas re-transplantation; $n=10$, PTA after ITX; $n=9$, PTA after kidney transplantation; $n=5$ and transplantation within the study period but the patients entered the programme before January 2010; $n=7$.

Out of a total of 61 ITXs performed during the study period in our centre, we included 25 cases in this study. The ITXs not included were mostly re-transplantation to patients who entered the programme before the study period; $n=31$. We excluded ITX after kidney transplantation; $n=3$ and ITX after PTA; $n=2$.

Immunosuppressive protocols

The immunosuppressive protocol for PTA patients included ATG induction (Thymoglobuline®, Genzyme) and maintenance therapy with tacrolimus (trough level 10–12 µg/L tapered to 6–10 µg/L after 8 weeks), mycophenolate mofetil (MMF) 1 g twice daily and steroids. We gradually tapered Prednisolone from 20 mg to 5 mg daily during the first 6 months after transplantation. A steroid-free immunosuppressive protocol for ITX patients included: ATG (Thymoglobuline®, Genzyme) or Basiliximab (Simulect®, Novartis) for induction in combination with Etanercept (Enbrel®, Pfizer) and maintenance therapy with tacrolimus (trough level 10–12 µg/L tapered to 6–10 µg/L after 8 weeks) in combination with sirolimus (trough level 10–15 µg/L tapered to 7–10 µg/L after 12 weeks) or mycophenolate (MMF 1 g twice daily).

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

Data collection

Patients were identified by a search through the outpatient lists of all involved clinicians. Patient characteristics were collected from medical charts from the initial transplant centre visit. Awareness for hypoglycaemic episodes was assessed by Gold and Clarke score (9, 10) and categorized as impaired if Clark score assessment gave four or more than 'R' responses and as unaware if eight out of eight 'R' responses were found. The national transplant waiting lists and transplant lists for PTA and ITX were analyzed in order to identify the outcome for included patients. For ITX patients, we report graft function 1 year post-transplant for patients who had received more than one ITX. When describing graft function, we chose to place the patients into one out of three categories after transplantation: *insulin-independent* when the graft was well-functioning without the need of glucose-lowering therapy, *partly function* when C-peptide levels were above detection level (>10 pmol/L) but the patients needed insulin treatment for glucose control or *graft failure* when C-peptide levels were below detection level and insulin treatment was needed. One year graft survival was found by data collection in medical charts of the transplanted patients. All βCRT candidates had measured GFR investigations, as part of the pre-transplant work up, performed locally with plasma clearance methods according to centre praxis, mostly 51Cr-EDTA. We do not rely on estimated GFR measures for the purpose of pre-transplant considerations.

Statistical analyses

Data analysis was performed using MS Excel (version 14; Microsoft) and statistical analyses using SPSS (version 25; IBM). Categorical outcomes were described using frequencies and proportions while continuous variables were described as mean ± s.d. or median (minimum–maximum) when appropriate. Group comparisons were performed by a 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

In total, 144 patients were evaluated for βCRT between 2010 and 2020. The mean ± s.d. age was 36.9 ± 10.5 years and 41% were male, BMI was 25.7 ± 11.5 kg/m^2 and HbA1c 8.8 ± 1.7% (73 ± 19 mmol/mol) (Table 1). The mean dose of insulin per day was 52.4 ± 26.4 units and mean duration of diabetes was 23.7 ± 11.5 years.

The given reasons for the patients to be referred, for the evaluation of βCRT, were episodes with severe hypoglycaemia (63%), severe hyperglycaemia (12%), fluctuating blood glucose levels (14%), very difficult treatable diabetes phenotypes (5%), loss of motivation for treatment adherence (3%), purging of insulin (1%), escalating secondary complications of diabetes (1%) and severe insulin resistance (1%). Overall, 56% of the patients had impaired awareness for hypoglycaemia and 31% had unawareness for hypoglycaemia when evaluated by Clarke score (10).

Characteristics of the patients listed for beta-cell replacement therapy

Out of the 144 evaluated patients, 92 were listed for transplantation (Table 1). The listed patients had a higher mean BMI, 26.0 ± 3.6 kg/m^2 vs 25.1 ± 0.3 kg/m^2

Table 1 Characteristics of patients referred for beta cell replacement transplantation 2010–2019.

	All *n* =144	Wait-listed *n* = 92, 64%	Not wait-listed *n* = 52, 36%	*P*-value
Age, years	36.9 ± 10.5	39.2 ± 10.1	33.9 ± 9.3	0.86
Male, rate (%)	41	43	37	0.42
HbA1c, %	8.8 ± 1.7	8.9 ± 1.6	8.9 ± 1.9	0.67
HbA1c, mmol/mol	72.9 ± 18.9	73.5 ± 17.7	73.9 ± 20.9	0.67
Diabetes duration, years	23.7 ± 11.5	26.3 ± 11.4	18.9 ± 10.2	0.45
Daily insulin dose, units/24 h	52.44 ± 26.4	56.5 ± 29.9	48.6 ± 22.4	0.55
BMI, kg/m^2	25.7 ± 4.2	26.0 ± 3.6	25.1 ± 5.3	0.004
Impaired awareness[a], rate (%)	56	65	38	<0.005
Unawareness[a], rate (%)	31	37	19	0.03
Hyperglycaemia as main concern, rate (%)	12	13	10	0.54
History of recurrent diabetic ketoacidosis, rate (%)	13	14	12	0.66

[a]Awareness for hypoglycaemic graded according to Clarke score evaluation (10)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

($P < 0.005$) and more patients had hypoglycaemia as the main course for referral, 72% vs 48% for listed vs non-listed ($P=0.005$). In addition, the listed patients more frequently had impaired awareness (65% vs 37%, $P < 0.005$) or unawareness of hypoglycaemia (39% vs 19%, $P=0.03$).

The main reasons for not being wait-listed for βCRT were: potential for further optimization of medical therapy (35%), not referred back for unknown reason despite the fact that indication for transplantation was found (32%), insufficient indication for transplantation (8%), significant psychiatric (13%) or medical (12%) contraindications.

The distribution of patient characteristics referred in Table 1 did not change substantially when the group of patients not referred back were removed from the analyses (not shown).

βCRT evaluation activity 2010–2020

Figure 2 illustrates the number of patients evaluated for βCRT per year in the period 2010–2020. The highest activity was registered in 2013 ($n=25$), thereafter a trend with decreasing activity was observed. Median (minimum–maximum) time from evaluation to listing for transplantation was 9 (0–74) months and the peak in number of wait-listed patients listed was noted in 2014. Median (minimum–maximum) waiting time was 6 (0–24) months for PTA patients and 7 (1–27) months for ITX patients and the overall highest transplant activity was registered in 2015.

Implication of the introduction of multidisciplinary team to βCRT evaluation

The acceptance rate for listing was 84% in the period 2010–2014 and 40% in the period 2015–2019 ($P < 0.005$). Patients evaluated in the period 2015–2019 had less often hypoglycaemia as the main concern for referral, compared with patients evaluated in the period 2010–2014 (49% vs 75%; $P < 0.005$).

When we compared the patients listed and not-listed for transplantation, in the period 2010–2014 with the period 2015–2019, we found no differences with regard to age, gender, HbA1c-level, diabetes duration, daily insulin dose, BMI or indication for βCRT (Table 2). Patients listed during both periods were older than those not listed. During the last period, the wait-listed patients had lower mean HbA1c 8.4 ± 1.2% (68 ± 13 mmol/mol) vs 9.1 ± 2.1% (76 ± 23 mmol/mol) ($P < 0.005$) and a longer duration of diabetes: 30.0 ± 13.8 years vs 18.3 ± 9.3 years ($P < 0.005$) than the not-wait-listed patients.

There was a non-significant trend to more patients being recommended to optimize medical treatment in the last period compared with the former period (41% vs 15%, $P=0.09$). The rate of patients with medical or psychiatric contraindications for transplantation was similar in the two time periods.

Characteristics of patients undergoing PTA vs ITX

Pre-transplant characteristics of the PTA and ITX patients are shown in Table 3. PTA patients were younger (mean age 38.2 ± 9.6 years vs 46.3 ± 9.5 years; $P=0.006$),

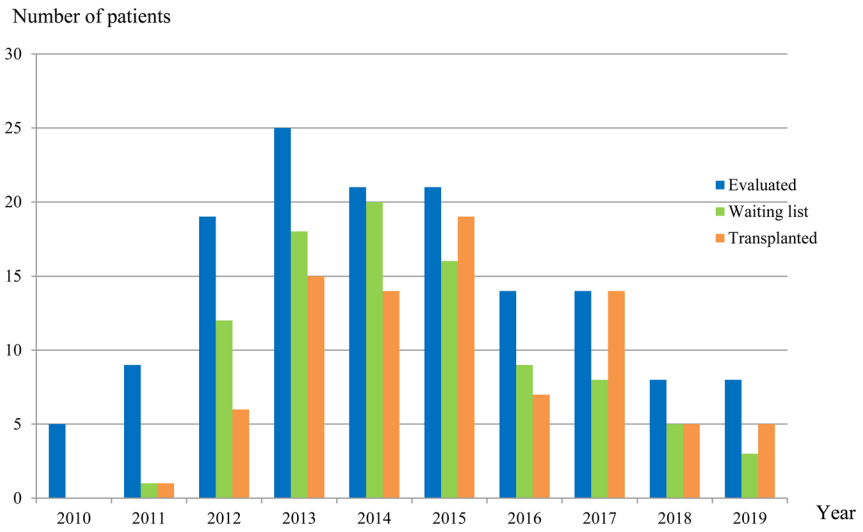

Figure 2
Distribution of the study population: numbers of new patients evaluated for βCRT, new patients listed for transplantation and number of patients receiving βCRT 2010–2019.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

Table 2 Characteristics of patients evaluated for beta cell replacement therapy 2010–2019: wait-listed vs not wait-listed for transplantation.

	All included, *n* = 144	All evaluated 2010–2014, *n* = 79	All evaluated 2015–2019, *n* = 65	*P*-value	Wait-listed 2010–2014, *n* = 66	Wait-listed 2015–2019, *n* = 26	*P*-value	Not wait-listed 2010–2014, *n* = 13	Not wait-listed 2015–2019, *n* = 39	*P*-value
Age, years	36.9 ± 10.5	36.8 ± 9.0	38.2 ± 11.3	0.69	37.6 ± 8.8	43.0 ± 11.9	0.09	31.8 ± 9.1	34.6 ± 9.4	0.19
Gender, rate men (%)	41	38	45	0.42	41	50	0.43	23	41	0.21
HbA1c, %	8.8 ± 1.7	8.9 ± 1.7	8.8 ± 1.8	0.33	9.1 ± 1.7	8.4 ± 1.2	0.11	8.3 ± 1.1	9.1 ± 2.1	0.39
HbA1c, mmol/mol	73 ± 19	75 ± 18	73 ± 19	0.33	76 ± 19	68 ± 13	0.11	67 ± 12	76 ± 23	0.39
Diabetes duration, years	23.7 ± 11.5	24.3 ± 10.5	23.3 ± 12.7	0.78	24.8 ± 10.1	30.0 ± 13.8	0.14	21.2 ± 13.1	18.3 ± 9.3	0.85
Insulin dose, units/24 h	52 ± 26	58 ± 32	49 ± 21	0.12	58 ± 34	52 ± 18	0.44	54 ± 21	47 ± 23	0.42
BMI, kg/m^2	25.7 ± 4.2	25.9 ± 4.2	25.3 ± 4.3	0.40	26.1 ± 3.8	25.7 ± 3.2	0.66	25.3 ± 6.2	25.0 ± 5.1	0.98
Hypoglycaemia, rate (%)	63	75	49	0.002	76	62	0.17	69	41	0.08
Impaired awareness[a], rate (%)	56	62	48	0.09	67	62	0.64	38	38	1.00
Unawareness[a], rate (%)	31	37	23	0.08	39	31	0.44	23	18	0.69
Hyperglycaemia, rate (%)	12	10	14	0.49	11	19	0.23	8	10	1.00
DKA, rate (%)	13	16	9	0.20	18	4	0.07	8	13	1.00

[a]Awareness for hypoglycaemic graded according to Clarke score evaluation (10).

had shorter duration of diabetes (24.9 ± 11.0 years vs 35.8 ± 10.7 years; $P = 0.01$) and needed higher insulin doses (0.8 ± 0.4 units/kg/day vs 0.6 ± 0.1 units/kg/day) than ITX patients. The mean measured GFR was comparable in the two groups.

One-year graft survival of pancreas transplant alone and islet transplant grafts

Seventy-three per cent of the PTA patients were independent of exogenous insulin 1 year after transplantation. Eight per cent had partial graft function while 19% had lost all graft function 1 year after PTA.

None of the ITX patients were independent of exogenous insulin 1 year after transplantation. However, 90% of the patients had partial graft function. Ten per cent had suffered from graft loss within the first year after transplantation. There was no difference in PTA or ITX graft survival in the period 2010–2014 vs 2015–2019.

Discussion

The main finding of this study is that the number of new patients referred for beta-cell replacement therapy in Norway has fallen after a peak in 2013.There was an increased focus and interest in βCRT in Norway after ITX was included as clinical treatment in 2009 and we altered the surgical technique for pancreas transplantation in 2012.

Since the peak in 2013, our numbers of PTAs have been reduced while the ITX activity has been more constant. These trends are in accordance with international reports (26, 27, 28, 29). This diversion of interest away from pancreas transplantation may be multifactorial. Stratta *et al*. lists several concerns for the situation in the US: improvement in diabetes management, improved insulin formulas, glucose sensors and insulin pumps and the promise of the artificial or bionic pancreas in addition to challenges in patient logistics (30).

We introduced MDT evaluation of βCRT candidates in order to enhance the quality of our selection of transplant patients and to improve patient education. Associated with the introduction of MDT evaluation was a reduced rate of patients wait-listed for transplantation falling from 84 to 40%. Interestingly, the introduction of psychiatric evaluation, as part of the MDT evaluation, did not affect the rate of patents with psychiatric contraindications for transplantation. Our experience is that early psychosomatic involvement in patients has increased the

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

Table 3 Pre-transplant characteristics of PTA and ITX recipients.

	PTA,[b] *n* = 74	ITX,[c] *n* = 12	*P*-value
Age	38.2 ± 9.6	46.3 ± 9.5	0.006
Gender, rate men	46	33	0.54
HbA1c, %	8.9 ± 1.7	8.4 ± 0.9	0.08
HbA1c, mmol/mol	74.4 ± 18.7	68.8 ± 9.8	0.08
Diabetes duration, years	24.9 ± 11.0	35.8 ± 10.7	0.01
Daily insulin dose, units/24 h	58.3 ± 31.3	39.4 ± 8.0	0.02
Daily insulin dose per bodyweight, units/kg/24 h	0.8 ± 0.4	0.6 ± 0.1	0.11
BMI, kg/m^2	26.2 ± 3.8	23.9 ± 2.1	0.08
Impaired awareness for hypoglycamia[a], rate (%)	68	58	0.54
Unawareness for hypoglycamia[a], rate (%)	39	25	0.52
Hyperglycaemia as main indication for TX, rate (%)	12	8	1.00
History of recurrent diabetic ketoacidosis, rate (%)	18	0	0.20
Measured glomerular filtration rate (mGFR)	98.7 ± 26.5	94.4 ± 22.8	0.63
1-year graft survival	–	–	<0.005
Independence from insulin, rate (%)	73	0	–
Partly graft function, rate (%)	8	90	–
No graft function, rate (%)	19	10	–

[a]Awareness for hypoglycaemic graded according to Clarke score evaluation (10). [b]Total PTA in Norway 2010–2019, *n* = 105. [c]Total ITX in Norway 2010–2019, *n* = 61.

focus of psychological issues and improved the follow up of post-transplant when present.

During the study period, there has been considerable improvement in diabetes treatment and technology for the management type 1 diabetes patients. Insulin pump technology has been upgraded to include multiple basal insulin infusion rates and patterns to deliver insulin boluses and bolus calculators have been integrated into the pumps to make it easier to individualize insulin treatment with different activities and meals (31). More importantly, the availability, cost and quality of continuous glucose monitors (CGMs) have improved significantly. The use of insulin pumps and CGMs were reported to be 33 and 45% among patients with type 1 diabetes in Norway in 2019 (32). Technological solutions which automate insulin delivery based on CGM data have documented superiority and are further evolving (33, 34, 35). Currently one hybrid closed-loop system is available on the Norwegian marked.

The advances in type 1 diabetes management are also reflected in our study. Patients referred to our centre for βCRT in the last part of the study period, had a lower mean HbA1c and fewer patients were referred due to hypoglycaemic episodes. In addition, a higher rate of patients was recommended to optimize medical treatment before transplantation could be considered in the last part of the study period. These findings can be explained by the increased availability of insulin pumps and CGMs throughout the study period through governmental reimbursement (32).

The technology for the management of type 1 diabetes is expected to continue its advance, but how this will affect the future need for βCRT is not known. Given the known risks from surgery and immunosuppressive therapy, optimization of non-surgical therapy should be preferred to transplantation in most patients. The introduction of the MDT in the evaluation of patients pre-transplant is probably of value, to improve and broaden this evaluation. The patient knowledge and consensus regarding treatment have been improved as the different specialists bring different aspects into the patient meetings.

In our selected patient population, 81% of the PTA and 90% of the ITX patients had partial or normal graft function 1 year after transplantation. It is now acknowledged in international consensus criteria that βCRT might be successful even if the patients are not independent of exogenous insulin (36). The achievement is to obtain stable and near to normal blood sugar in the absence of hyperglycaemic events, this is also conveyed to us by some of our patients declining supplemental islet transplants to reach insulin independence.

The present study is the first to describe in detail the selection process of βCRT candidates and the impact of MDT in this selection process. This is a single-centre report and may be biased by differences in referring criteria but should be found relevant for other centres in terms of organization of βCRT and selection of eligible patients.

The weakness in this study is the restricted follow-up data. We have graft survival results but do not have

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0519

follow-up data with quality of life data or hypoglycaemic score assessments. These measures should be included in future studies.

Conclusion

The numbers of patients that have been referred for beta-cell replacement therapy in Norway has declined during the last 10 years and the rate of acceptance for this treatment has been reduced after a multidisciplinary team evaluation was introduced for transplant candidate eligibility. We found that 81% of the PTA and 90% of the ITX patients had partial or normal graft function 1 year after βCRT.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution statement
E N researched data and wrote the manuscript. J P L helped to provide data and reviewed the manuscript. R K C reviewed the manuscript. A Å helped to provide data and reviewed the manuscript. K I B contributed to the discussion and reviewed the manuscript and R H reviewed the manuscript. T B B reviewed the manuscript. H S reviewed the manuscript. T G J contributed to manuscript writing and reviewed the manuscript.

References

1 Kelly WD, Lillehei RC, Merkel FK, Idezuki Y & Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* 1967 **61** 827–837. (https://doi.org/10.1097/00007890-196801000-00034)
2 Brekke IB. Indications and results of pancreatic transplantation: the Oslo experience 1983–1990. *Diabetologia* 1991 **34** (Supplement 1) S18–S20. (https://doi.org/10.1007/BF00587612)
3 Schive SW, Foss A, Sahraoui A, Kloster-Jensen K, Hafsah G, Kvalheim G, Lundgren T, von Zur-Mühlen B, Felldin M, Rafael E, *et al*. Cost and clinical outcome of islet transplantation in Norway 2010–2015. *Clinical Transplantation* 2017 **31** [epub]. (https://doi.org/10.1111/ctr.12871)
4 Horneland R, Paulsen V, Lindahl JP, Grzyb K, Eide TJ, Lundin K, Aabakken L, Jenssen T, Aandahl EM, Foss A, *et al*. Pancreas transplantation with enteroanastomosis to native duodenum poses technical challenges – but offers improved endoscopic access for scheduled biopsies and therapeutic interventions. *American Journal of Transplantation* 2015 **15** 242–250. (https://doi.org/10.1111/ajt.12953)
5 Lindahl JP, Horneland R, Nordheim E, Hartmann A, Aandahl EM, Grzyb K, Haugaa H, Kjosen G, Asberg A & Jenssen T. Outcomes in pancreas transplantation with exocrine drainage through a duodenoduodenostomy versus duodenojejunostomy. *American Journal of Transplantation* 2018 **18** 154–162. (https://doi.org/10.1111/ajt.14420)
6 Nordheim E, Horneland R, Aandahl EM, Grzyb K, Aabakken L, Paulsen V, Midtvedt K, Hartmann A & Jenssen T. Pancreas transplant rejection episodes are not revealed by biopsies of the donor duodenum in a prospective study with paired biopsies. *American Journal of Transplantation* 2018 **18** 1256–1261. (https://doi.org/10.1111/ajt.14658)
7 Nordheim E, Birkeland KI, Asberg A, Hartmann A, Horneland R & Jenssen T. Preserved insulin secretion and kidney function in recipients with functional pancreas grafts 1 year after transplantation: a single-center prospective observational study. *European Journal of Endocrinology* 2018 **179** 251–259. (https://doi.org/10.1530/EJE-18-0360)
8 Annual report Scandiatransplant, 2018. (available at: http://www.scandiatransplant.org/resources/AnnualScandiatransplantdatareport2018.pdf)
9 Gold AE, MacLeod KM & Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994 **17** 697–703. (https://doi.org/10.2337/diacare.17.7.697)
10 Clarke WL, Cox DJ, Gonder- Frederic LA, Julian D, Schlundt D & Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995 **18** 517–522. (https://doi.org/10.2337/diacare.18.4.517)
11 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R & Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 1998 **59** (Supplement 20) 22–33; quiz 34–57.
12 Montgomery SA & Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979 **134** 382–389. (https://doi.org/10.1192/bjp.134.4.382)
13 Maldonado JR, Dubois HC, David EE, Sher Y, Lolak S, Dyal J & Witten D. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT): a new tool for the psychosocial evaluation of pre-transplant candidates. *Psychosomatics* 2012 **53** 123–132. (https://doi.org/10.1016/j.psym.2011.12.012)
14 Folkman S & Lazarus RS. Stress-processes and depressive symptomatology. *Journal of Abnormal Psychology* 1986 **95** 107–113. (https://doi.org/10.1037//0021-843x.95.2.107)
15 Derogatis LR. *SCL-90. Administration, Scoring and Procedures Manual-I for the R(evised) Version*. Baltimore: John Hopkins University School of Medicine, Clinical Psychometrics Research Unit, 1977.
16 Goldberg DP. *A User's Guide to the General Health Questionnaire*, pp. 96–109. London: GL Assessment, 1988.
17 Snaith RP. The hospital anxiety and depression scale. *Health and Quality of Life Outcomes* 2003 **1** 29. (https://doi.org/10.1186/1477-7525-1-29)
18 Derogatis LR. The psychosocial adjustment to illness scale (PAIS). *Journal of Psychosomatic Research* 1986 **30** 77–91. (https://doi.org/10.1016/0022-3999(86)90069-3)
19 Wallston KA, Wallston BS & DeVellis R. Development of the multidimensional health locus of control (MHLC) scales. *Health Education Monographs* 1978 **6** 160–170. (https://doi.org/10.1177/109019817800600107)
20 Eysenck HJ & Eysenck SBG. *Manual of the Eysenck Personality Questionnaire (Junior and Adult)*. Kent, UK: Hodder & Stoughton, 1975.
21 Buss AH & Perry M. The aggression questionnaire. *Journal of Personality and Social Psychology* 1992 **63** 452–459. (https://doi.org/10.1037//0022-3514.63.3.452)

22 Bagby RM, Taylor GJ& Parker JD. Construct validity of the Toronto alexithymia scale. *Psychotherapy and Psychosomatics* 1988 **50** 29–34. (https://doi.org/10.1159/000288097)
23 Bagby RM, Taylor GJ & Parker JD. The twenty-item Toronto alexithymia scale – II. Convergent, discriminant, and concurrent validity. *Journal of Psychosomatic Research* 1994 **38** 33–40. (https://doi.org/10.1016/0022-3999(94)90006-x)
24 Berman AH, Palmstierna T, Källmén H & Bergman H. The self-report drug use disorders identification test: extended (DUDIT-E): reliability, validity, and motivational index. *Journal of Substance Abuse Treatment* 2007 **32** 357–369. (https://doi.org/10.1016/j.jsat.2006.10.001)
25 Babor TF, Higgins-Biddle JC, Saunders JB & Monteiro MG. *AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care*, 2nd ed. Geneva, Switzerland: World Health Organization, 2001.
26 Kandaswamy R, Stock PG, Gustafson SK, Skeans MA, Urban R, Fox A, Israni AK, Snyder JJ & Kasiske BL. OPTN/SRTR 2018 annual data report: pancreas. *American Journal of Transplantation* 2020 **20** (Supplement 1) 131–192. (https://doi.org/10.1111/ajt.15673)
27 Annual report NHS pancreas transplantation 2017–2018. (available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16776/nhsbt-pancreas-and-islet-transplantation-annual-report-2018-2019.pdf)
28 Annual Report Eurotransplant 2019. (available at: https://www.eurotransplant.org/wp-content/uploads/2020/06/Annual-Report-2019.pdf)
29 Annual report Australia and New Zealand Islet and Pancreas Transplant Registry 2019. (available at: http://anziptr.org/wp-content/uploads/2019/06/ANZIPTR-Annual-Report-2019.pdf)
30 Stratta RJ, Fridell JA, Gruessner AC, Odorico JS & Gruessner RW. Pancreas transplantation: a decade of decline. *Current Opinion in Organ Transplantation* 2016 **21** 386–392. (https://doi.org/10.1097/MOT.0000000000000319)
31 Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. *New England Journal of Medicine* 2012 **366** 1616–1624. (https://doi.org/10.1056/NEJMct1113948)
32 Annual Report Norsk Diabetesregister 2019. (available at: https://www.noklus.no/norsk-diabetesregister-for-voksne/)
33 Kowalski A. Pathway to artificial pancreas systems revisited: moving downstream. *Diabetes Care* 2015 **38** 1036–1043. (https://doi.org/10.2337/dc15-0364)
34 Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, Schoelwer M, Ruedy KJ, Jost E, Carria L, *et al.* A randomized trial of closed-loop control in children with Type 1 diabetes. *New England Journal of Medicine* 2020 **383** 836–845. (https://doi.org/10.1056/NEJMoa2004736)
35 Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, Acerini CL, Dellweg S, Benesch C, Heinemann L, *et al.* Home use of an artificial beta cell in Type 1 diabetes. *New England Journal of Medicine* 2015 **373** 2129–2140. (https://doi.org/10.1056/NEJMoa1509351)
36 Rickels MR, Stock PG, de Koning EJP, Piemonti L, Pratschke J, Alejandro R, Bellin MD, Berney T, Choudhary P, Johnson PR, *et al.* Defining outcomes for beta-cell replacement therapy in the treatment of diabetes: a consensus report on the Igls Criteria from the IPITA/EPITA Opinion Leaders Workshop. *Transplantation* 2018 **31** 343–352.

Received in final form 16 December 2020
Accepted 4 February 2021
Accepted Manuscript published online 6 February 2021