11th EPITA SYMPOSIUM & 40th AIDPIT WORKSHOP

ABSTRACT BOOK

[OP01]
ISLETS LOADED IN HYDROGEL DERIVED FROM HUMAN AMNIOTIC MEMBRANE (AMNIOGEL) REVERSE DIABETES IN IMMUNODEFICIENT MICE

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Background
Neovascularized devices and biopolymer scaffolds are getting a great deal of attention for their potential to improve islet transplantations. Among many biomaterials sources, human amniotic membrane (HAM) are considered as an inexpensive and natural source to produce ECM-based hydrogels with immunomodulatory, anti-inflammatory and antifibrotic properties. Herein, we develop an ECM-based hydrogel (Amniogel) derived from HAM and evaluate its potential to support islet function in vitro and in vivo.

Methods
The Amniogel were generated from HAM and accessed for porosity, for ECM content and, fiber integrity. The protein content in Amniogel and native HAM lysates were measured. To assess Amniogel impact on islet viability and function isolated rat islets were incorporated into the Amniogel and cultured for one week. The cell viability was evaluated by FDA/PI staining. To demonstrate islet function the glucose stimulated insulin secretion (GSIS) tests were performed using standard ELISA. Next, we assessed whether incorporation of islets into Amniogel could enhance engraftment and lead to better glycemic control in diabetic SCID mice. For this purpose 250 rat islets (IEQ) loaded into the Amniogel or Sigma rat tail Collagen or islets alone (control) were transplanted into the epididymal fat of diabetic SCID mice. Blood glucose levels were monitored daily and intraperitoneal glucose tolerance tests were carried out. Grafts and serum were harvested at 1, 2, 6 and 12 weeks to assess outcome.

Results
The ECM concentration in the hydrogel affected the pore size. Insulin expression and viability of islets incorporated into Amniogel was significantly higher than the islets loaded in commercial collagen or that of islets in free-floating culture. In addition, significant enhancement of GSIS was observed from islets embedded in Amniogel as compared to the two controls. In vivo experiments showed that, transplantation of 250 IEQ embedded in Amniogel lead to enhanced engraftment, vascularization, viability and better glycemic control compared to control mice transplanted with islets into commercial collagen or with islets alone.

Conclusions
Incorporation of pancreatic islet into amnion-derived Amniogel enhances islet engraftment and is a valuable approach to improve islet transplantation outcomes.

[OP02]
DEVELOPMENT AND APPLICATION OF THE NEWCASTLE PANCREAS ENDOCRINE STRESS SCORE (NPESS) FOR ULTRASTRUCTURAL ASSESSMENT OF PANCREATIC ISLET CELLS

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Objectives

Pancreatic islets are exposed to acute stress, from ischaemia during organ procurement and transport, as well as from the isolation process. This can impact upon transplantation outcomes. Greater understanding of sub-cellular changes in response to cell stress will enable informed development of interventions to improve survival and function of islet cells. We have recently developed and validated an electron microscopy score to assess acute changes in organelles of acinar cells in ischaemic donors. We aimed to implement this score for evaluating endocrine cells in tissue and isolated islets.

Methods

We analysed 30 donor pancreata, including 3 with T1D and 3 with T2D. 3 isolated islet preparations were evaluated. Tissue biopsies from pancreas head and tail, or isolated islets were processed for transmission electron microscopy (TEM). 11-25 endocrine cells were selected at random from each specimen for image capture and analysis. We analysed the severity of the changes in these cells, in alignment with the exocrine scores, additionally evaluating loss of endocrine vesicles. Using these images revealing the spectrum of ultrastructural appearances, we developed the NPESS, comprising 5 parameters each scored according to a 4-point severity scale to quantify organelle stress. Analyses of NPESS and the relationship with donor variables were then performed.

Results

Scores were highest (worst) for mitochondria (2.73±0.24) and lowest (best) for nuclei (0.79±0.52), with ER exhibiting the widest range of scores (1.47±0.67) (n=30). Total NPESS score positively correlated with NPASS (r=0.32, p=0.04, n=41). Total scores were similar in head (8.33±1.36, n=18) versus tail (8.32±1.17, n=23), and in DBD (8.33±1.38, n=21) versus DCD (8.18±0.69, n=9). In the pancreas head, scores increased at higher cold ischaemic times (Figure 1). No overt differences were seen in donors with diabetes. Islets immediately post-isolation and after 24h culture had lower scores relative to islets *in situ* (Table 1).

Conclusions

We show that NPESS can be used to quantify subcellular acute stress and identify varying effects upon organelles. The NPESS has potential for application in a range of experimental models to improve our understanding of the impact of ischaemia upon islet cells, and of interventions to prevent or reverse this.

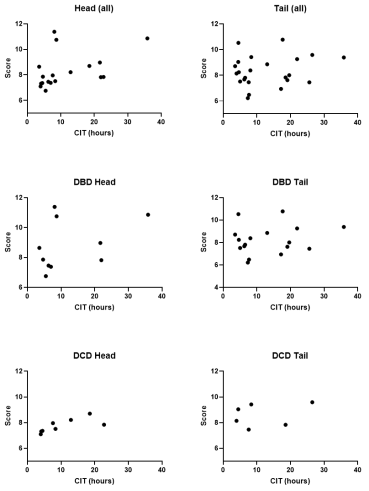

Figure 1. Correlations between total NPESS scores and CIT.
Total NPESS scores for each specimen are plotted against CIT of their respective organs. Scores correlated positively in the head of the pancreas (r=0.55, p=0.02), but no correlation was present in the tail (r=0.09, p=0.69). When stratified by donor type, the positive correlation in the head was lost for DBD donors (r=0.44, p=0.20) but persisted for DCD donors (r=0.81, p=0.02). There was no correlation in the tail for either DBD (r=0.05, p=0.84) or DCD (r=0.37, p=0.50) donors.

	Tissue			D0				D1			
	I-1	I-2	I-3	I-1	I-2	I-3	Tissue vs D0	I-1	I-2	I-3	Tissue vs D1
Nucleus	0.89	0.79	1.19	0.20	0.24	0.52	**p=0.008**	0.16	0.28	0.56	**p=0.02**
Mitochondria	3.00	2.86	2.38	1.96	1.90	1.56	**p=0.009**	1.28	1.44	1.40	**p=0.04**
Vesicle depletion	2.44	2.29	2.44	2.48	2.16	2.16	p=0.51	2.44	2.28	2.08	p=0.63
ER	1.11	0.85	1.79	0.44	0.28	0.40	p=0.14	0.56	0.80	0.64	p=0.35
Vacuolisation	0.94	0.86	1.38	0.60	0.84	1.08	p=0.28	0.64	0.80	0.96	p=0.23
Total	8.39	7.63	9.16	5.68	5.42	5.72	**p=0.03**	5.08	5.60	5.64	**p=0.04**

Table 1. NPESS scores are reduced in isolated islets when compared with matched pre-isolation endocrine tissue.
Individual organelle and total scores of pre-isolation tissue, islets immediately following isolation (D0), and islets following 24h of culture (D1), from three donor organs (I-1, I-2, I-3). A significant reduction in nucleus, mitochondria, and total scores was present at both D0 and D1 compared to islets *in situ*.

[OP03] GLUCOSE DURING IN VITRO PANCREATIC BETA CELL REGENERATION: FRIEND OR FOE?

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Objectives

The generation of pancreatic beta cells from human pluripotent stem cells can be an alternative source for beta cell replacement therapy. Different protocols for the in vitro generation of beta cells from stem cells have been developed over the years. The in vitro differentiation process has been performed under high glucose concentration conditions (≥ 20 mM) but its role is unclear. In this study, we investigated the effects of differentiating human induced pluripotent stem cells (hiPSCs) to insulin-producing cells (IPC) under physiological glucose concentration (5.5mM) compare to high glucose (20 mM).

Methods

The Babk2 hiPSC line was differentiated following a seven-stage protocol in Geltrex-coated cell culture plates (Rezania et al. 2014) with the experiment set in figure 1. Gene expression for beta cell transcription factors and markers were analyzed via RT-PCR. INSULIN, NKX6.1, PDX1, and ARX proteins were investigated by immunofluorescent staining followed by quantification analysis with Fiji.

Results

Differentiated Stage 5 to Stage 6 cells in 5.5mM glucose showed a 2.9 times higher expression of *NKX6.1* (P<0.001) compared to 20mM glucose. *GLUGACON, NEUROD1,* and *MAFA* expression were also significantly higher (P<0.05). Meanwhile, other endocrine-related genes such as *ARX, PDX1, INSULIN, NKX2.2,* and *SST* did not show significant changes to different glucose concentrations. An average of 52% INSULIN-positive cells co-expression with NKX6.1 in 5.5mM glucose at Stage 6 versus 12% co-expression in 20mM glucose (P<0.001). 95% of NKX6.1+ cells have co-expression with PDX1 compared to 21% in 20mM glucose (P<0.001). ARX and PDX1 co-expression have not been infected. Culturing cells in Stage 7 with 5.5mM glucose showed irreversible loss co-expression of NKX6.1/PDX-1, which might be due to the negative effect of high glucose concentration during Stage 5 to 6.

Conclusions

Our results showed that cells differentiated under physiological glucose concentration (5.5mM) express higher endocrine-related genes. Culturing cells with high glucose concentrations induced an irreversible reduction in the co-expression of PDX1/NKX6.1. Therefore, high glucose concentrations might not be beneficial for human iPSCs to IPC differentiation.

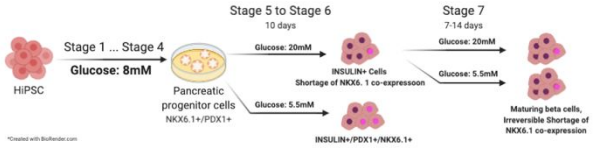

Figure 1. Experimental regimen.

[OP04] IMPROVING CD4+CD25+FOXP3+ TREG PERFORMANCES BY EX-VIVO EXPANSION IN THE PRESENCE OF IL-7 AND IL-15

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Objectives. Adoptive transfer of $CD4^{+}CD25^{high}FOXP3^{+}$ Treg (Treg) remains an attractive option to induce tolerance in the clinical transplant setting. Traditionally, Treg are expanded *ex-vivo* with αCD3-CD28 and high doses of IL-2. However, once transferred in humans the number of Treg rapidly decline within weeks, potentially limiting the therapeutic effectiveness of this approach. In order to improve the performance of Treg we set up an *in-vitro*

expansion protocol in which IL-2 is substituted with homeostatic cytokines IL-7 and IL-15.
Methods. Naïve Treg were FACS sorted $CD4^+CD25^+CD127^-CD45RA^+CD62L^+$ from peripheral blood (98% purity) and expanded *in vitro* using αCD3/CD28 coated beads at 1:1 ratio and in the presence of different combinations of IL-2 (100U/ml), IL-7 (10ng/ml) and IL-15 (5ng/ml). The final number of expanded Treg, the phenotype, the resistance to apoptosis and the capacity to persist in NSG mice was evaluated after 14 days of expansion.
Results. As compared to the standard expansion method with IL-2, Treg expanded in the presence of IL-7/IL-15 showed an increased capacity to expand (fold change: 135 IL-2 vs 193 IL-7/IL-15). The surface phenotype and expression of Treg markers were similar between Treg expanded with IL-2 or with IL-7/IL-15. Once expanded, Treg were put in culture without cytokines to mimic cytokine deprivation that is likely to occur after adoptive transfer. Treg expanded with IL-7/IL-15 showed a superior capacity to survive and expand after cytokine withdrawal *in vitro*. Preliminary results showed that once transferred into NSG mice Treg expanded with IL-7/IL-15 displayed an increased capacity to expand and persist *in vivo*.
Conclusions. *In vitro* expansion in the presence of IL-7/IL-15 generated Treg with improved performances in terms of expansion and survival in different conditions. These preliminary results provided a rationale to determine the therapeutic effectiveness of Treg expanded in the presence of IL-7/IL-15 in animal models of islet transplantation.

[OP05]
GENERATION OF B CELLS FROM IPSC OF A MODY8 PATIENT WITH A NOVEL MUTATION IN THE CARBOXYL ESTER LIPASE (CEL) GENE

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Background. MODY8 is a rare form of monogenic diabetes characterized by a mutation in *CEL* (carboxyl-ester-lipase) gene, which leads to exocrine pancreas dysfunction, followed by β cell failure. Induced pluripotent stem cells can differentiate into functional β cells. Thus, β cells from MODY8 patients can be generated *in vitro* and used for disease modelling and cell replacement therapy.
Methods and results. A genetic study was performed in a patient suspected of monogenic diabetes. A novel heterozygous pathogenic variant in *CEL* (c.1818delC) was identified in the Proband, allowing diagnosis of MODY8. Three MODY8-iPSC clones were reprogrammed from skin fibroblasts of the patient, and their pluripotency and genomic stability confirmed. All three MODY8-iPSC differentiated into β cells following developmental stages. MODY8-iPSC-derived β cells were able to secrete insulin upon glucose dynamic perifusion. *CEL* gene was not expressed in iPSC nor during any steps of endocrine differentiation.
Conclusions. Our study reported the existence of a novel pathogenic variant in the CEL gene, leading to MODY8, generated MODY8-iPSC that can be used as a tool for disease modelling studies and finally it showed that iPSC from MODY8 patient can differentiate into functional pancreatic β cells, opening the way to a potential future therapy of diabetes with β cells derived from autologous iPSC.

[OP06]
TRANSPLANTATION SITE INFLUENCE ON ISLET CELLULAR COMPOSITION

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Objectives: Transplantation (Tx) sites used for pancreatic islets (PI) were repeatedly compared according to blood perfusion, long term insulin secretion, etc. There are still some questions about hypoglycaemia induced glucagon secretion from PI Tx into the portal vein. We have focused on cellular composition of PI after Tx into the portal vein or into artificial subcutaneous (s.c.) pouches and compare it to native PI in pancreas.

Methods: Male Lewis rats (250-300g) served as PI donors and recipients. Diabetes was induced by intraperitoneal injection of streptozotocin (65 mg/kg) and only animals with glycemia over 20 mmol/l in three measurements were included into experimental groups. Marginal grafts consisting of 4 PI per gram of body weight were Tx to all recipients. In the group A (n = 7) PI were Tx into the portal vein, in groups B (n=7) and C (n=7) PI were Tx into the artificial cavity created using a macro-porous scaffold implanted s.c. for 12 (7 days scaffold + teflon inlay, next 5 days after teflon bar removal) or 28 days (7 days scaffold + teflon inlay), respectively. Function of grafts was monitored for 100 days until the samples for histology were harvested. The healthy animals were used as controls (n=4). All excised grafts and naive pancreases were fixed in 10% formalin and stained for immunofluorescence imaging using antibodies against insulin or glucagon. At least 20 PI were analysed in each group. The obtained immunofluorescence pictures were processed by ImageJ and total areas of alpha or beta cells were quantified using a colour thresholding and the ratio was calculated.

Results: Blood glucose levels of all diabetic recipients were normalized in two weeks after Tx and normoglycemia maintained until the end of experiment. The isolation and Tx processes, and a different environment for PI grafts influenced the α vs β cells composition of the graft in comparison to natural PI within the pancreas. The ratio of α to β cells has dropped from 13% in the pancreas to 7% in cavity D7+5, 3% in cavity D28+0, and 0,5% in the liver.

Conclusions: While alpha cells almost disappeared after Tx into the portal vein. The presence of alpha cells is much better preserved after Tx into the artificial s.c. cavity and similar to native composition of PI cells.

Acknowledgement: This work was supported by MH CR (DRO IKEM IN 00023001).

[OP07]
IMPACT OF SARS-COV-2 ON INTERNATIONAL PANCREAS TRANSPLANT ACTIVITY

World Pancreas Transplant Covid Collaborators: Sivesh K Kamarajah*, Helmut Arbogast, Thierry Berney, Ugo Boggi, Julien Branchereau, Socci Carlo, Daniel Casanova, Matthew Cooper, Martin Drage, Doruk Elker, Joana Ferrer, Lucrezia Furian, Rainer Gruessner, Simon Harper, Artur Kwiatkowski, Takashi Kenmochi, Derek Manas, Emmanuel Morelon, Jon Odorico, Robert Oellinger, Gabriel Oniscu, Marcelo Perosa, Frantisek Saudek, Joseph Scalea, Peter Schenker, Bob Stratta, Fabio Vistulo, Pablo Uva, Steven A White

Objectives
The recent SARS-CoV-2 (COVID-19) pandemic has led to significant disruptions to healthcare delivery including transplantation. Although the impact of COVID-19 on liver and renal transplant activity is reported it remains less clear for pancreas transplantation.

Methods
An online survey covering key areas for pancreas transplant services was developed and disseminated via the World Pancreas Transplant Guidelines Group between May and July 2020.

Results
A total of 28 respondents from 28 centres and 16 countries spanning four continents completed the online survey. Most respondents were transplant surgeons (n = 15, 53.6%), followed by hepatobiliary, pancreatic and transplant surgeons (n = 28, 28.6%), and general surgeons (n = 5, 17.9%). This survey highlights the significant reduction in pancreas transplant referrals being in excess of 75% in nearly 40% of all centres. There had been a decrease in

utilization of donor after cardiac death (DCD) and donor after brain death (DBD) donors from 46.4% to 7.1%. In the UK during the months of March to April 2020 total organ retrievals were down by over 95%. Both donors and recipients were screened for COVID-19 with 92.8% of centres opting for PCR nasopharyngeal swab testing. With respect to induction therapy, there were reduced frequency of use of standard dose ATG (64.3% to 42.9%), standard-dose Campath (21.4% to 10.7%) with an increase in dose-reduced ATG (14.3% to 17.9%) and Simulect (14.3% to 25.0%). Centers did not report any significant changes to maintenance therapy which largely included tacrolimus, mycophenolate mofetil, prednisolone and sirolimus.

Conclusions
This international survey demonstrates a high level of variation in managing pancreas transplant services during the COVID-19 pandemic. These data highlight the management challenges and several practice variations in caring for these patients alongside government variations in how to manage a serious viral pandemic. Dissemination of data from this survey will go some way to help improve our understanding of current international clinical practice during the COVID-19 pandemic.

[OP08]
PANCREAS TRANSPLANTATION DURING THE COVID-19 PANDEMIC. A SINGLE CENTRE'S EXPERIENCE

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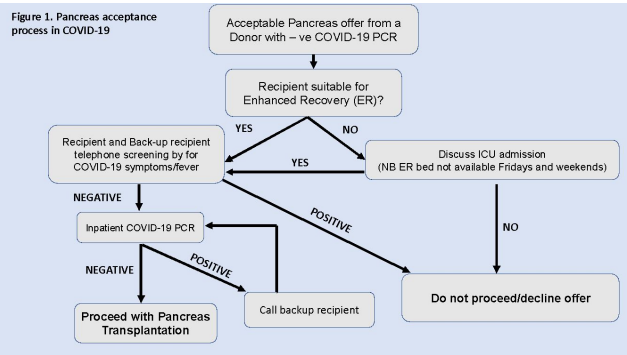
Objectives
The ongoing COVID-19 pandemic has led to significant reduction in pancreas transplantation (PT) activity. On 9th March 2020, we suspended 64 patients on our PT waiting list, excluding 4 highly sensitized patients eligible for kidney transplantation. The primary reasons for suspension were the perceived risk with the use of alemtuzumab (lymphocyte depleting induction) and constrained access to intensive care.
Our PT program successfully resumed on 4th August 2020 through the adoption of new strategies and creative resource management. We share our experience as well as the clinical outcomes of the first cohort of 13 discharged patients transplanted during the pandemic.

Methods

A. We created a central operating group (COG), a multidisciplinary team that met regularly and were solely tasked with resuming PT in safe manner whilst fitting into competing hospital resources
B. We capitalised on our strengths namely being situated in "Covid-19 free" hospital site and were able to predict a seamless resumption due to the ongoing operational infrastructure maintained by the kidney transplantation program
C. Patients were updated regularly and encouraged to continue sending monthly blood samples for tissue typing
D. Enhanced Recovery (ER) was created to ease demands on ICU capacity, an area of beds in surgical recovery supported by both recovery and transplant nurses to provide level 2 (HDU) care
E. Using outcomes from pre-COVID-19 PT data we were able to select recipients suitable for ER and define a PT acceptance process **(figure 1)**
F. We revised our donor and recipient characteristics criteria to improve transplantation rates and outcomes
G. We gained support from microbiology to provide 24 hr rapid COVID-19 PCR access (CEPHEID GeneXpert)



Results

Our donor and transplant recipient demographics and outcomes are summarised in table 1.

Table 1. Donor and transplant recipient demographics and outcomes

Parameter (mean ± STD)	13 transplants
Transplant type (SPK/PTA)	12/1
Donor Age, years	37.4 ± 11.9
Donor Type (DBD/DCD)	9/4
Donor BMI	21.9 ± 3.7
Donor Girth (cm)	78.2 ± 7.2
Recipient Age, years	43 ± 10
Recipient Sex (M/F)	6/7
Recipient BMI	24.7 ± 3
RRT HD/PD/Predialysis	6/4/2
Number of HLA mismatches	3.6 ± 1
Mean Calculated Reaction Frequency	12.8 ± 12.9
Cold ischaemia time, hours	10.9 ± 1.8
Kidney DGF rate (%)	1/12 (8%)
Return to theatre during initial admission	0%
Functioning grafts at discharge	100%
Length of hospital stay, days	11.9 ± 3.8
Number of days since transplant, mean (range)	73 (21 - 98)
Acute Rejection episodes	1/13 (7%)
Readmission in 30 days	3/14 (21%)
Complications*	5/14(29%)
SARS-CoV-2 positive recipients to date	0

*Complications (n = 5)
1) Suspected SPK rejection, readmitted and treated with high dose methylprednisolone
2) Readmission with mechanical small bowel obstruction requiring laparotomy
3) Readmission with acute kidney injury from dehydration and vomiting
4) Readmission with acute kidney injury from dehydration and
5) Clostridium difficile infection managed with antibiotics and supportive care.

Conclusions

Our early results following our rigorously revised PT program provides evidence that we can continue pancreas transplantation into the second COVID-19 wave with alemtuzumab induction without exposing our patients to additional risks.

[OP09] IMPACT OF COVID-19 SELF-QUARANTINE MEASURES ON BEHAVIOUR, STRESS, ANXIETY AND GLYCAEMIC CONTROL IN PATIENTS WITH B-CELL REPLACEMENT THERAPY

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Objectives

Patients with severely complicated type 1 diabetes (T1D) who receive β-cell replacement therapy have multiple risk factors for a severe course of coronavirus disease, including use of immunosuppression (IS). Quarantine strategies implemented due to the COVID-19 pandemic are known to impact both mental and physical health, but this impact is expected to be even greater in patients at high risk for a severe course of COVID-19. We therefore aimed to investigate the behavioural, mental and physical implications of the nationwide quarantine in pancreas and islet transplant recipients.

Methods

To be able to study the effect of the quarantine on glycaemic control, all patients with T1D who had received a transplantation with islets or a non-optimally functioning pancreas (i.e. with a marginal β-cell mass) using IS were eligible. As a control group, patients with T1D without IS were included. Using questionnaires, self-quarantine behaviour and self-reported changes in anxiety, stress, physical activity, weight and glycaemic control were assessed. HbA1c during quarantine was compared to the last measurement before quarantine.

Results

Transplant recipients (n=51, age 55 (IQR 48 – 59) years, BMI 23.3 (20.9 – 27.4) kg/m^2, diabetes duration 42 (34 – 48) years) adhered more stringently to quarantine measures compared to patients with T1D (n=272, age 53 (37 – 62) years, BMI 25.2 (23.0 – 27.8) kg/m^2, diabetes duration 27 (15 – 39) years). In transplant recipients compared to T1D, 52.1% vs 18.3% (p=0.000) reported not going out for groceries and 45.8% vs 14.0% (p=0.000) reported not leaving the house at all. Fear of coronavirus infection was higher in transplant recipients (VAS 5.0 (3.0 – 7.0) vs 3.0 (2.0 – 5.0), p=0.004) and glycaemic control worsened during quarantine (ΔHbA1c +1.67±8.74 vs -1.72±6.15 mmol/mol (p=0.006)). Among transplant recipients, 26.8% reported increased insulin use, 40.0% less physical activity, 41.7% weight gain, 29.2% increased anxiety and

33.3% increased stress since the start of quarantine.

Conclusions
Quarantine due to the coronavirus pandemic has significant impact on behaviour, physical activity, weight, stress, anxiety and glycaemic control in patients after β-cell replacement therapy. Health care professionals should be aware of these changes to be able to provide extra support.

[OP10]
NORMOTHERMIC REGIONAL PERFUSION INCREASES PANCREAS GRAFT UTILISATION AFTER DCD ORGAN DONATION

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Objectives
Organ donation by DCD (deceased after cardiac death) occurs after a patient is deemed to have encountered a non-survivable insult to the brain that does not meet brain stem death criteria[1,2], this accounts for 40% of all organ donation in the UK[1]. There is reluctance by centres in the UK to accept pancreata from DCD donors due to the reduced organ recovery compared to the DBD (deceased after brain death) donors, with a national average decline rate of 45% (23-100%) across all centres[1,2]. NRP (normothermic regional perfusion) is a novel method of organ preservation, which restores oxygenated blood in situ thus reducing the ischaemic injury too donor organs[3,4]. Promising results have been demonstrated in graft survival and recovery in liver and kidney recipients and overall organ utilisation[2,6] We review our past 5 year experience with DCD-NRP and demonstrate increased pancreas utilisation compared to DCD alone.

Methods
Single centre retrospective analysis of local and NHSBT data. All multi-organ retrievals performed by our centre from 2015 were reviewed. We compared the utilisation of pancreas graft following DCD-NRP versus DCD alone. A paired t -test was conducted to compare age in the 2 donor groups. Chi χ^2 with Yates correction analysis performed to compare DCD-NRP to DCD for organ utilisation.

Results
Our centre performed 366 DCD multi-organ retrievals from the period of February 2015 to October 2020. 41 DCD donors proceeded where the pancreas had been offered and accepted. There were 11 NRP-DCD retrievals and 30 standard DCD retrievals. The mean age of the DCD-NRP group was 33 and 44 in the DCD-NRP group (P=0.015). In the 11 DCD-NRP retrievals performed 7 pancreas were utilised as whole organs as simultaneous pancreas kidney transplants, 2 for islet transplant and 1 for simultaneous kidney and islet transplant, 1 pancreas was reviewed by the recipient centre and deemed not suitable after back table dissection. In the DCD alone group 27 were not accepted for either pancreas or islet transplant. 3 were deemed suitable for implant (1 SPK and 2 islets). DCD-NRP was shown to increase utilisation of pancreas grafts compared to DCD alone (91% vs. 10%, p<0.0001).

Conclusion
DCD-NRP organ retrieval increases pancreas utilisation compared to DCD alone, providing a novel method for increasing the pancreas donor pool.

[OP11]
OUTCOMES OF SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTS FROM DONATION AFTER CIRCULATORY DEATH DONORS IN THE UK: A NATIONAL REGISTRY ANALYSIS

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Objectives
The UK is a world leader in the use of pancreases from donation after circulatory death (DCD) donors. However, there is a perception that pancreases from DCD donors are sub-optimal when compared to similar grafts from donation after brain death (DBD) donors. We compared outcomes of pancreases transplanted from controlled DCD donors to those from DBD donors in the largest reported study to date.

Methods
Data were obtained from the UK Transplant Registry on deceased donor adult SPK transplants between 2005 – 2018. Kaplan-Meier estimates were used to compare pancreas, kidney, and patient survivals between those receiving organs from DCD or DBD donors, and multivariable analyses were used to identify factors associated with pancreas graft loss.

Results
2,228 SPK transplants were implanted (1825 DBD; 403 DCD donors). Kidneys from DCD donors had equivalent graft survivals to those from DBD donors (Figure 1. p=0.99), and there were no differences in longer-term renal allograft function, or in five-year patient survivals when stratifying by donor type. On univariate analysis, there were no significant differences in five-year death-censored pancreas graft survival between the two donor types (Figure 2. 79.5% versus 80.4%; p=0.86). Multivariable analysis showed no significant differences in five-year pancreas graft loss between transplants from DCD (n=343) and DBD (n=1492) donors (hazard ratio 1.26, 95% CI 0.76-1.23; p=0.12). A Cox proportional hazards regression model for pancreas graft loss from DCD donors showed that increasing donor age or pancreas cold ischaemic time (CIT) were not associated with worse outcomes.

Conclusions
This large national study supports the increased utilisation of organs from DCD donors in SPK transplantation within the UK and globally. Data on the effects of donor age and CIT on DCD donor graft outcomes will inform national pancreas offering schemes.

[OP12]
THE EFFECT OF DONOR DIABETES-ASSOCIATED GENOTYPES ON OUTCOMES AFTER PANCREAS TRANSPLANTATION.

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Objectives: Identifying predictors of long-term pancreas transplant outcomes is crucial for optimising organ selection and improving patient survival. The effects of donor associated diabetes risk on pancreas graft outcomes are unknown. The aim of this study was to investigate whether donor HLA-DR3, HLA-DR4 and HLA-DR3/DR4 heterozygosity, which are strongly associated with autoimmune diabetes, are associated with poorer pancreas transplant outcomes.
Methods: This was a single centre retrospective study of 919 pancreas transplants (721 simultaneous pancreas-kidney [SPK], 130 pancreas transplant alone [PTA] and 68 pancreas after kidney [PAK]) performed at the Oxford Transplant Centre between 2003 and 2019. Data were requested from NHSBT and Oxford Transplant Immunology. For each operation type (i.e. SPK, PTA and PAK), death-censored Kaplan-Meier and Cox regression analyses were performed to assess the impact of the diabetes-associated HLA types on graft and patient survival.
Results: Donor HLA-DR3 and donor HLA-DR3/DR4 heterozygosity showed no association with graft and patient survival in our analyses. In contrast, the presence of donor HLA-DR4 was associated with reduced PTA transplant survival (p=0.010). Furthermore, in a multivariate analysis, with operation type included as a covariate, donor HLA-DR4 was confirmed as a negative predictor of pancreas graft survival (p=0.039; hazard ratio [HR], 1.379; 95% confidence interval [CI], 1.017-1.870). Donor HLA-DR4 had no effect on patient

survival and, in SPK recipients, it had no effect on kidney graft survival.
Conclusions: For the first time, this study has demonstrated that the presence of diabetes-risk HLA-DR4 in donors correlates with reduced pancreas transplant survival, particularly for PTA recipients.

[OP13]
ISLET CELL ISOLATION AND TRANSPLANTATION FROM DCD DONORS IN SCOTLAND

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The Scottish Islet Transplant Unit has performed over 300 islet isolations and transplanted over 60 patients from donors after brainstem death (DBD) and donors after circulatory death (DCD). Pancreas utilisation from DCD donors remains low compared with other organs and there is concern that islets from DCD donors may yield poorer isolations and function. This study examines the quality and clinical outcomes of islet cell isolations from DCD donors compared to DBD donors.

We compared the yield, purity and viability of isolations from DBD and DCD donors and their subsequent utilisation for transplant. We examined clinical outcomes in recipients that received either their 1st or 2nd transplant from a DCD donor and compared them to recipients of islet transplants from DBD donors. Student t-test was used for all comparisons.

271 DBD and 65 DCD isolations were performed and there were no significant differences in mean yield (248800 vs 213713, p=0.18), viability (81.9% vs 81.4%, p=0.88), and purity (69.3% vs 71.6%, p=0.58). There was also no significant difference in the utilisation rate for clinical transplant (33.9%% DBD vs 30.7% DCD). All patients that received islet transplants from either DCD or DBD donor that had at least one year's follow-up data were then analysed. 15 patients (DCD group) received one or more islet transplants from a DCD donor (7 DCD:DBD, 6 DBD:DCD, 2 DCD:DCD). 25 patients received 2 islet transplants from DBD donors (DBD group). There were no significant differences in mean total IEQ/kg between the DCD and DBD groups (9489 vs 9049, p=0.34). There were also no significant differences in donor demographics (age, weight, BMI, CIT). Clinical outcomes were excellent in both the DBD and DCD groups and there were no significant differences in 1 year graft survival (84% vs 87%), stimulated c-peptide (671 vs 580pmol/L, p=0.54), number of severe hypoglycaemic events/yr (0.04 vs 0.28, p=0.25), HbA1C (56 vs 52mmol/mol, p=0.25) and median beta score (3 vs 3, p=0.21). Awareness of hypoglycaemia was superior in the DBD group compared to the DCD group (Gold Score 2 vs 4, p<0.01).

Islet cell isolations from DCD pancreases have equitable yield, purity, viability and clinical function compared to DBD pancreases. DCD pancreases are an underused resource that have the potential to increase the availability of islet cell transplant.

[OP14]
LINEAR RELATION BETWEEN PRIMARY ISLET GRAFT FUNCTION AND 5-YEAR OUTCOME OF IT: A SINGLE CENTER RETROSPECTIVE COHORT STUDY IN 39 PATIENTS

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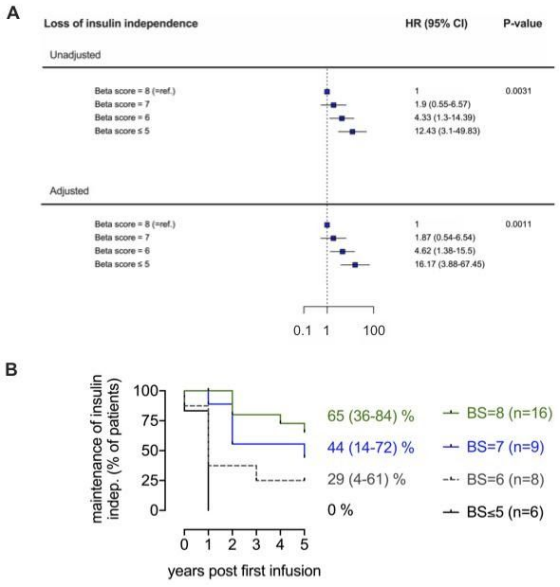
Objectives
Long-term outcome of Islet Transplantation (IT) in T1D varies and optimizing the probability of long-term success is a major

issue. In other organ transplantations like kidney or liver, early allograft dysfunction is an independent predictor of overall survival graft. In this single-center retrospective cohort study, we explored the relation between primary islet graft function (PGF) and 5-year outcomes of IT.

Methods
Participants were 39 T1D patients recruited from three clinical trials (NCT00446264/NCT01123187/NCT01148680) with severe hypoglycemia and/or a functioning kidney graft, who received intraportal IT. Exposure of interest was PGF, measured one month after last islet infusion with categorical (beta-score, BS) or continuous (beta2-score, B2S) clinical validated indexes. Primary outcome was maintenance of insulin independence with HbA1c <6.5%, and secondary outcomes were IT metabolic outcomes at 5 years. Association of outcomes with PGF and prespecified covariates (recipient type, immunosuppression regimen, and total islet mass transplanted) were also analyzed.

Results
A total of 39 patients with 20(51%) of females, mean age of 45±8 years were enrolled in the study. Primary outcome was linearly and incrementally associated with PGF measured with categorical beta-score (p=0.001). Patients with a BS of 8 had 16.13 (3.88-66.67) (p=0.0001) more chances to maintain insulin independence through the 5-year follow-up than patients with a BS ≤5 (adjusted HR (95%CI), BS ≤5 as reference) (**Figure 1**).
PGF measured with continuous B2S was associated with maintenance of insulin independence through the 5-year follow-up, with a HR (95% CI) of 1.99 (1.27-3.13) per 5 unit increase of B2S and independently from other covariates. All 5-year metabolic outcomes were also linearly and incrementally associated with PGF categories.

Conclusions
This study showed a significant and robust association between PGF and long-term outcome following allogenic IT for T1D. Importantly, this relation appeared linear and independent from other known predictors. Furthermore, PGF was also linearly associated with more refined variables derived from CGMS.



[OP15]
ISLET TRANSPLANT OUTCOMES IN THE INTEGRATED UK PROGRAMME

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Objectives

Islet allo-transplantation for type 1 diabetes has been fully commissioned by the National Health Service in the UK since 1 April 2008 and fully integrated within the national offering scheme since the end of 2010. Our aims were to assess islet transplant activity and islet function, measured by key variables: graft survival, reduction in HbA1C, insulin requirements and annual rate of severe hypoglycaemic events.

Methods
Data were obtained from the UK Transplant Registry on islet transplant activity between 1 April 2010 and 31 March 2020. Metabolic outcomes and Kaplan-Meier graft survival are reported at one-year post-transplant for the period, 1 April 2010 to 31 March 2019 and five-year graft survival for the period 1 April 2008 to 31 March 2019.

Results
On 29 February 2020, 28 patients were on the UK active islet transplant list, 12 (43%) were waiting for a simultaneous islet and kidney (SIK) transplant. For patients registered between 1 April 2014 and 31 March 2018, median waiting time to islet transplant was 464 days (95% confidence interval 269-659 days).

There were 275 islet transplants, including 19 SIK, performed in 164 patients in the ten-year time period. In 2019/20, 28 islet transplants were performed, almost three-times that performed in 2008/09 when first commissioned.

Following solitary islet transplantation, 1 April 2010 to 31 March 2019, in the year post-transplant of the 108 patients with reported hypoglycaemic data, 89 (82%) experienced no severe hypoglycaemic events with the remaining 19 (18%) experiencing between one and nine events. At one-year post transplant compared with prior to transplant, there was a reduction in median daily insulin dose from 0.48 to 0.26 units/kg and a reduction in HbA1C from 64 to 51 mmol/mol.

The estimated one-year graft survival after solitary islet transplantation, was 87%. Five-year graft survival, 1 April 2008 to 31 March 2019, was 51% overall: 33% for patients receiving one routine graft only, compared with 60% for patients receiving one routine and subsequent top-up grafts, p<0.0001.

Conclusion
Comprehensive reporting within a centrally commissioned, audited and governed national scheme provides high-quality data confirming good one-year graft survival and metabolic outcomes and five-year graft survival better with a subsequent top-up graft than without.

[OP16]
SALVAGING A PANCREATIC ALLOGRAFT FOR ISLET ALLO-AUTOTRANSPLANTATION

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Objectives

Complications after pancreas transplantation may lead to a transplantectomy. Performing islet isolation and allo-autotransplantation (IAAT) may rescue endocrine function. Here we describe the early outcomes in patients after IAAT.

Methods

Three patients with type 1 diabetes and a simultaneous pancreas-kidney transplantation underwent an (emergency) pancreas transplantectomy. Immediately following resection of the pancreas allograft, the organ was flushed with UW-fluid and transported to the islet isolation facility for clinical islet isolation. Islets were infused via a percutaneous transhepatic procedure into the portal vein.

Results

Patient 1 is a 39-year old female who underwent a transplantectomy of the pancreas graft on post-operative day 10 because of a bleeding from an infected aneurysm of the arterial anastomosis. The islet yield was 480.000 IEQ from an oedematous and partly necrotic graft. After 1 year, HbA1c was 32 mmol/mol Hb (5.2%) with insulin 12 IU/day, without severe hypoglycemic events.

Patient 2 is a 52-year old female with recurrent bleeding at the anastomosis leading to a transplantectomy on post-operative day 20. From this partly fibrotic graft with a necrotic tail, 543.000 IEQ could be isolated and transplanted. 1-year HbA1c was 35 mmol/mol (5.5%) with insulin 20 IU/day, without severe hypoglycemic events.

Patient 3 was a 51-year old male with a pancreas transplantectomy 2 years after SPK. The islet yield was 716.000 IEQ. The patient was prescribed a daily dose of 1000mg metformin and 53 IU of insulin. Due to treatment inadherence both in the short and long term, HbA1c increased from 37 mmol/mol pre-operatively to 83 mmol/mol 6 months after IAAT.

In all patients, the final islet products were tested positive for bacterial cultures. However, no infectious complications occurred after IAAT.

Conclusions

Good glycemic control and absence of severe hypoglycemic events can be achieved with IAAT. Despite contaminated islet products, no complications were seen after transplantation. IAAT is a viable method to rescue endocrine function when a pancreas transplantectomy is indicated.

[OP17]
IMPACT OF HLA DONOR SPECIFIC ANTIBODIES IN THE ERA OF CELL THERAPY: CLINICAL TRAJECTORIES IN ISLET TRANSPLANTATION ILLUSTRATE A CHALLENGING MODEL.

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Objectives: Islet transplantation is a unique paradigm in the case of organ transplantation, since allogenicity is reputed to rely the most on cellular-mediated rejection. As multiple injections and donors are required to achieve complete insulin-independence, preformed or *de novo* DSA may target one or several donor islets. Considering the number of possible combinations between donors and DSA, the objective was to discriminate in our population illustrative clinical trajectories which can occur after transplant.
Methods: Patients included were type 1 diabetes patients transplanted in Lille, between the 01/01/2005 to the 31/12/2018. Only patients with available sera tested by Luminex during their whole follow-up were analyzed. Class I and II anti-HLA antibodies were determined by the LABScreen Mixed Luminex flow bead assay (One Lambda). In case of positivity, specificities and mean fluorescent intensity (MFI) were determined according to the LABScreen Single Antigen Luminex flow bead assay (One Lambda). MFI was considered as high when above 3000.
Results: 32 patients had a complete HLA antibodies screening during their whole follow-up. Among them, 8 patients presented with DSA. The presence of DSA was not associated with the risk of insulin-dependence at 4 years post-transplant (OR= 7.00 95CI[0.57– 126, p=0.13]). 5 combinations were identified according to the MFI-value, and the presence of preformed DSA, de novo DSA, or both. To simplify, we provide specific patient-based trajectories considering an islet transplantation with 1- high MFI preformed DSA, 2- high MFI de novo DSA, 3- low-MFI preformed or de novo DSA, 4- a

de novo DSA which becomes a preformed DSA because of multiple islet infusions, and 5- the specific case of Islet-after-Kidney transplantation. Only the 2nd trajectory was associated with poor outcomes.
Conclusions: The management of DSA in the context of islet transplantation is complex considering the number of possible combinations. We provide here illustrative clinical-based trajectories to facilitate type 1 diabetic patients cares.

[OP18]
COGNITIVE IMPACT OF IMMUNOSUPPRESSIVE TREATMENTS AFTER ISLET TRANSPLANTATION: A CASE-CONTROL STUDY

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Objectives: Allogeneic islet transplantation is a safe alternative for those patients with type 1 diabetes (T1D) who have severe hypoglycaemia complicated by impaired hypoglycaemia awareness or glycaemic lability, common sources of memory complaints. Islet transplantation implies an extended immunosuppression based on sirolimus or mycophenolate mofetil (MMF), associated to tacrolimus. Islet transplantation, immunosuppressive treatments, blood glucose balance can influence cognitive functions (*Reijnders MRF, Nat Commun, 2017, Bürker BS Clin Transplant 2017, Pflugrad H Plos One 2020*). The aim of this study was to compare a cognitive rating scale: MMSE (Mini Mental State Examination) between T1D with or without islet transplantation and to identify parameters influencing MMSE.
Methods: This case-control study compared MMSE and cognitive function tests between T1D patients with islet transplantation carried out between 2003 and 2020 and a control group of islet-transplant candidates for T1D. Exclusion criteria was patient refusal.
Results: 43 patients were included: 9 T1D controls (group 1) and 34 islet-transplanted patients, 14 receiving MMF (group 2) and 20 receiving sirolimus (group 3). MMSE score and other cognitive function tests were not different between the 3 groups (p= 0.70). In the global population (n=43), MMSE score was negatively correlated to HbA1c (r=-0.30; p= 0.047) and to the time spent in hypoglycemia on the CGMS (r=-0.32; p= 0.04). No correlation was found between MMSE score and C-peptide or the time spent under immunosuppressive treatment.
Conclusion: This first study evaluating cognitive function in islet-transplanted T1D patients did not show any difference when compared to non-transplanted controls or according to the type of immunosuppression. MMSE score seems more correlated to the quality of blood glucose control, especially the time spent in hypoglycemia, than to the type or duration of immunosuppressive treatment.

[OP19]
IMPACT OF INSULIN THERAPY IN PANCREAS TRANSPLANTATION DONORS ON GRAFT OUTCOMES: AN ANALYSIS OF THE OPTN/UNOS DATABASE

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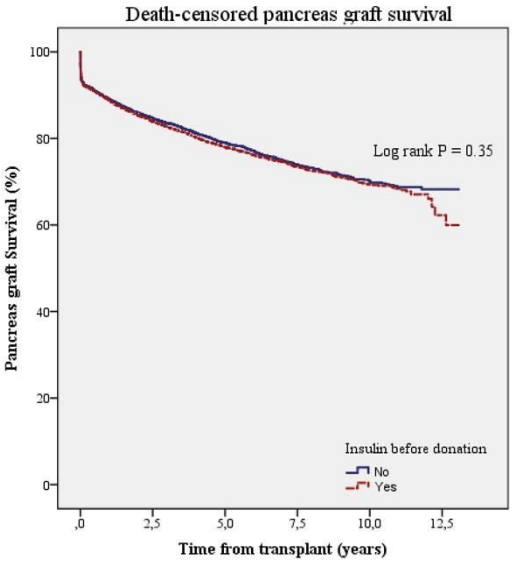
Objectives: Hyperglycemia requiring insulin treatment is frequent in critically ill patients and potential pancreas donors. Information on the impact of donor insulin use on pancreas outcomes is scarce. Thus, we explored the influence of donor insulin use on recipient and pancreas graft survival.

Methods: retrospective study with 12841 pancreas recipients (either simultaneous pancreas-kidney, pancreas after kidney or pancreas alone) from the OPTN/UNOS registry performed between 2000 and 2017. Multivisceral recipients other than simultaneous pancreas-kidney, those transplants from a donor < 30 kg and recipients with diabetes other than type 1 or 2 were excluded. Insulin donor requirements were defined as the need for any dose of insulin within 24 hours prior to donation.

Results: a total of 7765 (60%) patients received a pancreas from a donor with insulin requirements. Pancreas graft survival (death-censored) at 1 year was similar between those who received an insulin-requiring donor and the remaining (89% vs 89%, $P > 0.05$), as well as at 5 and 10 years (78% and 69% vs 79% and 70%, respectively, $P = 0.35$)(Figure). Donor insulin therapy was not associated neither with an increased risk of recipient death (HR 0.93 [95% CI 0.80-1.07], $P = 0.29$) nor pancreas graft failure (HR 1.08 [95% CI 0.99-1.17], $P = 0.09$).

Conclusions: insulin requirements in a potential pancreas donor is not associated, *per se*, with an impaired pancreas graft and patient survival. Thus, donors who require insulin therapy may be suitable for pancreas transplantation.



[OP20] DEVELOPMENT OF EX VIVO NORMOTHERMIC PERFUSION AS AN INNOVATIVE METHOD TO ASSESS PANCREASES AFTER PRESERVATION

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OBJECTIVE

Static cold storage (SCS) is the standard method for pancreas preservation but does not facilitate objective organ assessment prior to transplantation.
Normothermic machine perfusion (NMP) has been used to test other abdominal and thoracic organs' function and viability in transplantation settings. Our aim was to develop a NMP protocol specific for pancreases and then investigate its potential as an organ assessment strategy.

METHOD
8 porcine pancreases were procured in conditions replicating donation after circulatory death with warm ischaemia time of 25 minutes. After 3 hours of static cold storage (SCS) the pancreases were divided into 3 experimental groups 1) the feasibility group (n=2) that underwent 2.5 hours of NMP 2) the SCS group (n = 2) that underwent an additional 6 hours of SCS prior to assessment on NMP for an hour and 3) the Oxygenated Hypothermic Machine Perfusion (oxyHMP) group (n = 4) that underwent 6 hours of oxyHMP followed by 1-hour assessment on NMP.
The NMP protocol used autologous, leucodepleted blood delivered at a mean arterial pressure of 40mmHg with a temperature of 37°C.
At timed intervals during NMP, perfusate samples were collected for gas analysis and perfusion parameters were recorded.

RESULTS
The feasibility group was used to develop the NMP protocol and demonstrated stable perfusion parameters throughout NMP. Compared to the SCS group the oxyHMP group demonstrated better average perfusion characteristics with lower resistances, higher flow rates, lower mean lactate levels and physiological pH. The oxyHMP group maintained normal macroscopic appearances during NMP. At the end of NMP the SCS group had an average 32% weight increase compared to the oxyHMP group that were found to have a 17% weight reduction.

CONCLUSION
Normothermic machine perfusion of whole pancreases is feasible after cold preservation and potentially useful as an assessment strategy. Furthermore, it demonstrated that oxygenated HMP may be beneficial for pancreas preservation compared to SCS.

[OP21]
POST-TRANSPLANT MALIGNANCIES AFTER SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION: IMPLICATIONS ON LONG-TERM OUTCOME FROM A SINGLE-CENTER PERSPECTIVE

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OBJECTIVES: The advancement of immunosuppressive regimens paved the way for widespread implementation of solid organ transplantation as treatment of choice for end-stage organ failure by significantly improving patient and graft survival. However, long-term immunosuppressive therapy is associated with a high risk of malignancy. Simultaneous pancreas-kidney (SPK) transplant recipients require particularly high doses of immunosuppression. The main objective of this study is to evaluate the incidence and effect of de-novo malignancies after SPK transplantation in a high-volume center.
METHODS: 484 consecutive first SPK transplants at the Medical University of Innsbruck performed between 1985 and 2015 were evaluated for this study. After

exclusion of patients lost to follow-up (n=46) and patients where follow-up data was not complete (n=90) 348 patients were included in the final analysis. Chi-square tests and rank-sum tests were applied as appropriate. Kaplan-Meier-Plots, log-rank test and cox proportional hazard regression adjusted for donor and recipient factors were used to analyse patient and graft survival.

RESULTS: Of the 348 patients included in this study, 71 (20.4%) developed a post-transplant malignancy. Median time to diagnosis was 130 months. Thirty-six patients (50.7%) developed skin cancers. Solid organ malignancy occurred in 25 (35.2%), hematologic malignancy in 10 patients (14.1%). Affected patients were more frequently male (81.7% vs. 62.5%). No differences in induction therapy were seen. Both groups demonstrated comparable patient and graft survival. In comparison to patients with skin cancer, SPK recipients with solid and hematologic malignancies had a 3- and 6-fold increased hazard of death, respectively (aHR 3.04 [IQR 1.17-7.91], P=0.023; aHR 6.07 [IQR 1.87-19.71], P=0.003). When compared to patients without malignancies hazards of death were similar to those with solid and hematologic cancers. Patients with skin malignancies had a significantly decreased risk of death (aHR 0.37 [IQR 0.18-0.76], P=0.007).

CONCLUSIONS: Malignancies after SPK transplantation are common. Development of post-transplant cancer per se is not associated with decreased patient or graft survival. Differences, however, exist between different types of malignancies.

[OP22]

PANCREAS TRANSPLANTATION IN BLACK ASIAN AND ETHNIC MINORITIES- A SINGLE CENTRE EXPERIENCE IN THE UK.

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Objective:

It is reported that ethnic disparities in the outcomes after SPK transplantation still exist. The influence of ethnicity on the outcomes of pancreas transplantation in the UK has not been studied. We therefore investigated the influence of ethnicity in patients undergoing pancreas transplantation at our center.

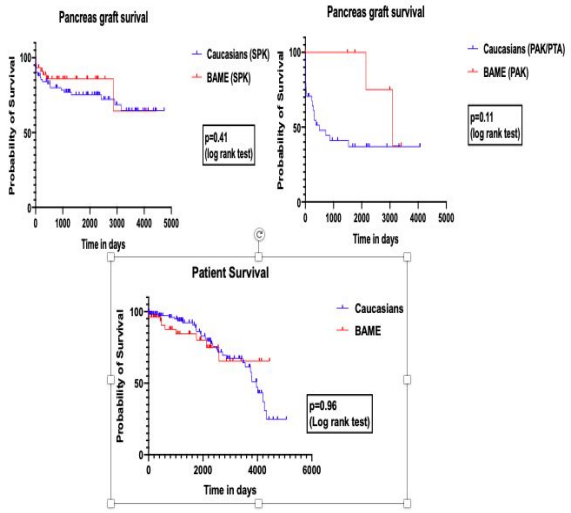
Methods:

A retrospective analysis of 171 pancreas transplant (SPK/PAK/PTA/ Re-transplants) recipients (Caucasians=118/ Black Asian Ethnic Minorities, BAME=53) from 2006 to 2020 was done. The median follow-up was 80 months. Patient & graft survival, rejection rate, steroid free maintenance rate, HbA1C, weight gain & the incidence of secondary complications of diabetes post-transplant were compared between the groups. After Holm-Sidak correction for multiple comparisons, p <0.003 = significant. Immunosuppression consisted of alemtuzumab induction and steroid free maintenance with tacrolimus and MMF.

Results:

There was no difference between the groups in terms of donor age, donor BMI, proportion of DCD donors, proportion of sensitized recipients (CRF>5%), HLA mismatches, recipient age and proportion of PAK/PTA. Caucasians had all re-transplants (n=11) & BAME had no PTA. We noted equivalent pancreas graft & patient survival in BAME (Fig 1). BAME had more % of type-2 DM pre-transplant (BAME=30.19% vs. Caucasians=0.85%, p<0.0001), and had similar access to transplantation once waitlisted (Median waiting time, Caucasians=232 days vs. BAME=217 days, p=0.96), although, Caucasians had a higher % of pre-emptive SPK transplantation (Caucasians=78.5% vs. BAME=0.85%, p<0.0001). Despite equivalent rejections & steroid usage, BAME gained more weight (Median % weight gain, BAME=7.7% vs. Caucasians=1.8%, p=0.001) but had similar HbA1C (functioning grafts) at 3,12, 36- & 60-months post-transplant. Caucasians had a higher incidence of secondary complications of diabetes (Caucasians=33.8% vs. BAME=13.5%, p=ns).

Conclusions:
BAME & Caucasians had comparable overall patient and pancreas graft survival. BAME had a higher proportion of pre-transplant type 2 DM and had similar access to transplantation once waitlisted, although there was a higher proportion of pre-emptive SPK transplantation in the Caucasians. Despite equivalent rejections & steroid usage, BAME gained more weight.



[OP23]
LIVE OXYGENATION MONITORING DURING HYPOTHERMIC OXYGENATED PERFUSION (HOPE) ON PANCREAS: A PRECLINICAL FEASIBILITY EVALUATION

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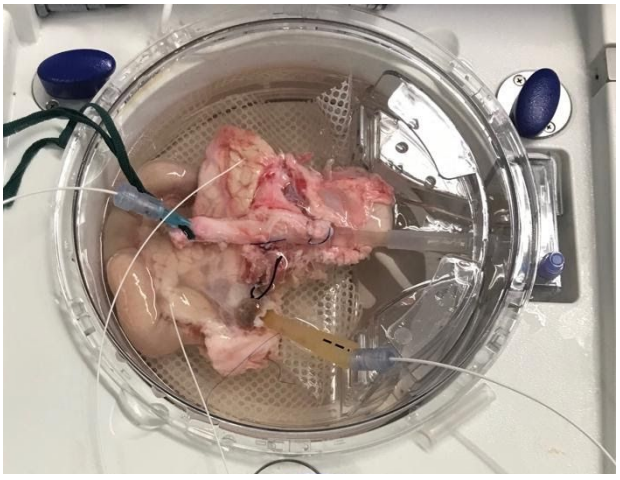
- Objectives

The objectives of our study is to establish a model of continuous oxygenation monitoring which will allow both to evaluate the efficiency of the different oxygenation modalities but also to provide a clinical objective of intra-tissue oxygenation.

- Methods

On porcine model from animal house, after pancreas procurement, the pancreatic transplant is prepared on a back-table with the placement of an arterial cannula in the aorta and of a venous cannula in the portal vein. The pancreas is placed on a hypothermic perfusion machine (WAVES system, IGL) with perfusion via the arterial cannula. The venous cannula flow is bypassed before going back to the cassette in order to collect sample directly from the veinous flow. To assess the intra-tissue oxygenation, we use fiberoptic probes custom made with 250 um of optical fibre (CP-004-001; Oxford Optronix, Abingdon, UK), inserted directly in the tissue (head and tail of the pancreas, aorta, portal vein). These fiberoptic probes allow simultaneous measurement of tissue PO_2, laser Doppler flux (as an index of tissue perfusion) and tissue temperature and allow monitoring of these parameters throughout the perfusion. Liquid of perfusion is oxygenated by the oxygenation of the wave cassette.



- Results

There is a high correlation between perfused oxygen and the intra-tissue partial pressure of oxygen in the head and tail of the pancreas. At each stage of oxygen flow, intra-tissue oxygenation evolves and reaches a plateau. When oxygen therapy is stopped, the oxygen partial pressure in the pancreatic tissue and portal vein is gradually reduced to 0. The continuous measurement of the partial pressure in arterial and venous 02 can assess the oxygen consumption of

the transplant. The repetition of the experiments could lead to the realization of abacus to establish a clinical objective of oxygenation.

Pa02 (kPA)	02 95%, 5L/min	02 95% 15L/min	No oxygenation
Head of the pancreas	0,3	0,6	0,1
Tail of the pancreas	4,5	7,3	0,1

- Conclusions

Partial pressure in oxygen appears to be a reliable, precise and reproducible measurement to evaluate HOPE for pancreatic preservation. This assessment could also be a good way to control oxygenation during pancreas normothermic perfusion.

[OP24]
UNEXPLAINED FEVER AFTER PANCREAS TRANSPLANTATION: CHARACTERISTICS AND LONG-TERM OUTCOMES.

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Objectives: Unexplained fever (UF) after pancreas transplantation is an observed complication but poorly known and little described. The objectives of our study were to describe the prevalence and characteristics of UF among pancreas recipients, to identify its risk factors and analyze its impact on long-term outcomes.
Methods: All patients who underwent a pancreas transplant (with or without kidney) in our center from January 2010 to December 2019 were included. Patients with early pancreas thrombosis were excluded. UF was defined as fever with undetermined cause despite clinical, biological, imaging and microbiological exams.
Results: On 232 patients, 44 (19%) experienced UF. UF patients statistically had a lower BMI (22.0 kg/m^2 vs. 23.1 kg/m^2, p = 0,008), and their donors were younger (27 vs. 31.2 years, p = 0.008). Fever started at mean at 22.5 (+/- 6.6) days after the transplantation and lasted 7.8 (+/- 6.2) days. It was associated with elevated CRP levels (88.8 +/- 56.5 mg/L at mean) without elevation of serum lipase. Seventeen patients (39%) were treated with probabilistic antibiotic therapy which did not influence duration of fever or hospitalization length for fever. No difference was found concerning patients' nor pancreas and kidney transplants' survival.
Conclusion: After a pancreas transplant, nearly one in five patients has an UF between3 and 4 weeks after the transplantation. Its course is spontaneously favorable and not modified by probabilistic antibiotic therapy. UF has no impact on patient or graft survival. Its mechanism is not yet known but seems to be well related to the pancreatic transplant because it is not observed in patients with early transplantectomy or in other organ transplants.

[PP01]
ISLET CELL INTERACTIONS INFLUENCE THE DYNAMIC OF INSULIN SECRETION

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Objectives: Pancreatic islets are composed of different cell types, which are submitted to paracrine and direct intercellular interactions. Understanding the role of these interactions in the function of the islets will open a new avenue for the development of innovative therapeutic approaches to diabetes treatment. In the present work, we aimed to study the influence of different pseudoislet cellular compositions on insulin secretion.

Methods: In a first approach, isolated rat islets were dissociated into single-cells and FACS sorted to obtain purified beta cells, non-beta cells (including alpha and delta cells) and alpha cells. Sorted cells were seeded into microwells for the formation of different types of pseudoislets (PSI): 1) beta cells only, 2) beta-cells and non-beta cells (ratio 2:1), 3) beta cells and alpha cells (ratio 2:1). In a second approach, PSI were generated with cell lines 1) mouse insulin-secreting MIN6 cells and 2) MIN6 and mouse glucagon-secreting alphaTC1 cells (ratio 2:1). After formation, PSI were placed into perifusion chambers for the assessment of dynamic insulin release and were tested in parallel by static incubation in basal or glucose-stimulated conditions.

Results: PSI composed of beta cells and non-beta cells showed a lower first and second phase insulin secretion as compared to PSI composed of beta cells only. Static incubation performed on replicates confirmed this trend. By contrast PSI formed with beta cells and alpha cells showed a similar or even an increased insulin secretion as compared to PSI made of beta cells, either with perifusion assay or with the static incubation method. Interestingly, PSI made of both MIN6 and alphaTC1 cells displayed a better insulin secretion as compared to PSI made of MIN6 cells only, both in static incubation and perifusion assays.

Conclusions: Our results suggest that the nature of the islet cellular composition can impact beta-cell function. Indeed, according to our preliminary results, insulin secretion can be influenced by the function of cells others than alpha cells, such as somatostatin-secreting delta-cells.

[PP02]
HUMAN AMNIOTIC EPITHELIAL CELLS IMMUNOMODULATORY PROPERTIES ARE ENHANCED BY IFN-G, AND PROTECT ISLETS AGAINST INFLAMMATORY CYTOKINES

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Introduction: Inflammation is a primary contributor to early graft loss and poor islet engraftment. Human amniotic epithelial cells (hAEC) possess regenerative, immunomodulatory and anti-inflammatory

properties. In particular, these cells express HLA-G and HLA-E, involved in immunomodulation and immune tolerance. Here, we hypothesized that hAECs could protect islets from cellular damage induced by pro-inflammatory cytokines and we assessed the cytokine-induced expression of HLA-G and HLA-E in hAECs.

Methods: Rat islets were cultured with or without hAECs for 24 hours, followed by 48-hour exposure to IFN-γ, TNF-α and IL-1β. Controls included mono or cocultures without cytokines. For all conditions, glucose stimulated insulin secretion (GSIS), apoptosis by detection of histone-associated DNA fragments, and Th1/Th2 cytokines secreted in the culture media were evaluated by ELISA. Gene expression modifications were assessed by qPCR. hAEC surface marker expression (CD105, CD90, CD326, HLA-E, HLA-G, SSEA-4) was assessed by flow cytometry after culture in control culture medium or in medium containing various concentrations of human recombinant IFN-γ for 24–48H.

Results: Exposure to a pro-inflammatory cocktail significantly increased the secretion of the anti-inflammatory cytokines IL6, IL10 and G-CSF by hAECs at both 24H and 48H. IL6, IL8 and IL10 gene expression was significantly upregulated, as well as HLA-G and HLA-E. This correlated with an upregulation of STAT1, STAT3 and NF-κB1gene expression levels. RI co-cultured with hAECs maintained a normal insulin secretion after cytokine exposure compared to RI cultured alone, and a significantly lower apoptosis rate.

Conclusion: In conclusion, hAECs increase their anti-inflammatory and immunomodulatory potentials when exposed to inflammation in vitro, and protect pancreatic islets against pro-inflammatory cytokines in a coculture set-up.

[PP03]
BIOSYNTHETIC ACTIVITY DIFFERS BETWEEN ISLET CELL TYPES AND IS MODULATED BY GLUCOSE AND OTHER SECRETAGOGUES

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Objectives:
In addition to the secretory activity, the biosynthetic activity is essential for the long-term function of islet cells in culture and possibly also after islet transplantation. In this work, we addressed the questions of whether biosynthetic activity differs between the different islet cell types and how it changes according to glucose and other secretagogues.

Methods:
Rat islet cells were exposed to 2.8 or 16.7 mM glucose, in absence or presence of 3-isobutyl-1-methylxanthine (IBMX), phorbol myristate acetate (PMA) or diazoxide. Biosynthetic activity was assessed by adding O-propargyl-puromycin (OPP) that incorporates into newly translated proteins. After cell fixation, OPP was chemically ligated to a fluorescent dye by "click" reaction, and labeling was analyzed by fluorescence microscopy. The different islet cell types were identified by immunofluorescence using specific antibodies. Fluorescence intensity (OPP labeling) was quantified at the single cell level using the ImajeJ software.

Results:
Fluorescent OPP labeling was observed in all islet cell types and under all conditions tested. Heterogeneous biosynthetic activity was observed between the four islet cell types, with delta cells showing the higher relative protein biosynthesis. All islet cell types displayed an increase of biosynthesis in response to glucose. IBMX and PMA, known to stimulate insulin secretion, had no similar effect on protein biosynthesis. Finally, diazoxide was used to prevent glucose-mediated insulin secretion and had no effect on protein biosynthesis

Conclusion:
Heterogeneous biosynthetic activity was observed between the four islet cell types, with delta cells showing the higher relative protein biosynthesis. All islet cell types displayed an increase of biosynthesis in response to glucose, with alpha cells showing the strongest response. IBMX and

PMA, known to stimulate secretion, had no similar effect on protein biosynthesis. Altogether, these results suggest that mechanisms regulating secretion and biosynthesis in islet cells are different, and that this OPP labeling approach is a promising method to assess biosynthetic activity in vivo and particularly in transplanted islets.

[PP05]
THE RESULTS OF ISLET AFTER KIDNEY TRANSPLANTATIONS FROM THE ISLET TRANSPLANTATION PROGRAM AT MEDICAL UNIVERSITY OF GDAŃSK IN POLAND.

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Objectives
We analyzed first clinical results of islet after kidney transplantation in patients with brittle type 1 diabetes in our new islet transplant program.
Methods
All islet infusions performed since October 2018 were analyzed.
Results
Five patients in age of 41, 53, 55, 51, 42 received their first percutaneous intraportal islet infusions over 2019, whereas the first patient also received subsequent second infusion. In 4 patients indication for ITx were recurrent severe hypoglycemia episodes (SHE) and in one problematic hyperglycemia. Patients received on average islet mass of 378,952 IEQ (318,585 – 491,643), with 5,750 IEQ/kg (5064 – 6636) suspended in 7.5 ml (1.3 – 13) of pellet. In addition to ongoing maintenance immunosuppression for kidney transplant, patients received either Thymoglobuline in case of first ITx or basiliximab in case of second ITx, with etanercept. β-cell graft function assessed on day 75 post after ITx was good/marginal, according to Igls criteria with complete elimination of severe hypoglycemic episodes, HbA1c improvement from 8.7 to 6.7%, 7.0 to 5.7%, 7.4 to 6.2%, 10.4 to 7.6% respectively, and 30-50% reduction in insulin requirements in 4 patients with a history of SHE. Currently, all four patients who received only a single islet infusion have no detectable c-peptide and the daily insulin requirement went back to baseline values. The only patient who received two subsequent islet infusions has stable islet function with HbA1c of 5.9%. It was impossible to perform subsequent islet infusions in all patients, all beta cell transplantations programs were paused in mid-March due to the COVID -19 pandemic with no activity across Poland until end of July 2020. Beta-cell replacement has been slow to re-establish across Poland, even in centers that remained open to other organ transplantation during the pandemic. There is an urgent need to address on-going constraints to restore an effective islet transplantation program.
Conclusions
Currently we are working to re-initiate the islet transplantation program at Medical University of Gdańsk in Poland.

[PP06]
VALIDATION OF NEW COOLING PROTOCOL ON COBE2991 AND EVALUATION OF ITS IMPACT ON GMP FACILITY

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Background:
The present study was performed to develop a new good manufacturing practice (GMP) compatible cooling system for the COBE 2991 aiming to optimize the purification of human islet cells using a cooled Cell Processor.
Materials and Methods:
We designed a new cooling system using AirJet™ XR40 connected to the COBE 2991 cell separator. Pressurized medical air at 5 bar and cooled at (-30˚C) was blown onto the rotor of COBE 2991 through a hole drilled in the plexiglass of its lid of the Cobe. During the purification process, temperatures of liquids were recorded at different steps, and the impact of the new COBE cooling system on a grade C clean room was assessed in GMP facility by monitoring both 0.5 and 5 µm particle emission at rest and during activity.
Continuous density gradient centrifugation was performed with or without the cooling system with light (1.061 g/ml) and heavy (1.084 g/ml) gradients. Due to the limited availability of pancreatic donors in Qatar, buffy coat from Bone Marrow tissue was tested according to our GMP standard protocol. Purity and viability of MNC mononuclear cell fraction were assessed using flow cytometry and hematology analyzer.
Results:
The newly designed cooling system significantly decreased the temperature in the Cobe from 18˚C to a window of 0-5˚C during the first steps of cell separation, and could maintain the temperature of collected fractions between 4 to 5˚C. Linear gradients were achieved and a high percentage of MNC fraction (98%) was recovered with 100±2% post processing viability using the dye 7-amino-actinomycin-D and 98% with Trypan Blue.
Particle counting at rest and in operation were significantly below the GMP standards for 0.5 and 5 µm size particles (Class C).
Conclusion: Continuous density gradient separation of human islets or bone marrow tissue to MNC in a cooled environment is both feasible using the affordable AirJet™ XR40 cooling system on COBE2991 and compatible with GMP standards.

[PP07]
FROM PANCREAS WAITING LIST TO TRANSPLANT A LONGITUDINAL QUALITATIVE STUDY

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Objectives
There are limited studies of the patient experience regarding pancreas transplant and research in pancreas transplant is heavily weighted towards the quantitative and biomedical approach to study. This study took a qualitative approach of the pancreas patient experience of pancreas transplant. This is a longitudinal study which follows the patient experience from waiting list to transplant. In the understanding of this experience the hope is to inform future practice and potential interventions as well as identify further areas for study and development.

Methods
The study investigates patients listed for Simultaneous Pancreas and Kidney (SPK) transplant in Edinburgh. All recipients on the SPK waiting list for one year were eligible. Data was collected using semi-structured qualitative interviews of an average 30 min duration. This was initially face to face, then following COVID restrictions via video. These were transcribed and analysed using NVIVO and a Constructive Grounded Theory approach (Charmaz,2017). The study was longitudinal in design, the first interview being conducted when there is an estimated 6 months to transplant and the second 3 months post-transplant.

Results
The initial findings from this study are from 10 interviews with 7 patients, 7

pre-transplant and 3 post transplantation. The participants: 3 males and 4 females, 3 pre-dialysis and 4 on dialysis, 6 patients were working and 1 unemployed.
The main findings from the data analysed identified that the experience of chronic disease causes suffering. However, although the disease maybe the same the experience of each individual is diverse. All participants showed experiential avoidance of diabetes in their glycaemic control and there is a surprising intrigue pre – transplant and a period of adaption to the space left by diabetes post- transplant.

Conclusions
The individualistic experience of suffering reiterates a need for person-centred care, as the process of alleviating suffering can only be started once identifying the cause. Living with a chronic disease is challenging and experiential avoidance can be damaging and irreversible. Successful pancreas transplant creates a void in the removal of an all-encompassing disease.

Charmaz K.(2017) Constructivist grounded theory *The Journal of positive psychology* 12(3) pp299-300

[PP08]
A REVIEW OF GASTROPARESIS SYMPTOMS POST SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANT AND UTILISATION OF CURRENT NUTRITIONAL PROTOCOL.

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Objectives:

Assessment of data to determine:
- Gastroparesis symptoms post simultaneous pancreas and kidney transplant (SPK).
- Utilisation of current nutritional protocol post SPK.

The influence of nutritional status on postoperative morbidity and mortality has been highlighted in many studies. Gastroparesis can affect nutritional status in this patient group pre transplant however little research has been carried out on the presence of symptoms post transplant.

Methods:

Retrospective assessment of data from March 2018 – September 2020 of patients admitted to the Royal Infirmary of Edinburgh who underwent an SPK transplant.
All patients had a dietetic assessment pre transplant and were categorised into a high or low risk group. High risk patients were identified as requiring early nasojejunal (NJ) feeding post transplant and low risk patients were offered oral nutritional supplements (ONS).
The presence of gastroparesis was highlighted in pre transplant assessment and the presence of symptoms reviewed post transplant.

Results:

Date range	**March 2019 – Sept 2020**	**March 2018-March 2019**
Total number of patients	28	12
% patients identified as high nutritional risk	36% (n=10)	50% (n=6)
% of high risk patients who had NJ placed	60 % (n=6)	33% (n=2)
% of high risk patients who received NJ feed > 1 day	20% (n=2)	33% (n=2)
% of high risk patients who reported gastroparesis pre transplant	90% (n=9)	83% (n=5)
% of patients with gastroparesis who reported **no** symptoms post transplant *	77% (n=7)	80% (n=4)

**Subjective reporting of symptoms.*

Conclusion:

- 77 – 80 % of patients report resolution of gastroparesis symptoms post transplant.
- In the patient group who report ongoing gastroparesis symptoms 33 % report an improvement in symptoms.
- Recommended that further research in this area is carried out using a validated tool.
- 20 - 33 % of high risk patients are following the current SPK nutritional protocol recommendation of post transplant NJ feeding. There have been no adverse effects reported and no increased length of stay in the high risk group who did not received NJ feeding.
- Pre transplant assessment enables us to identify those at high risk of malnutrition and implement preoperative interventions thus potentially reducing the need for NJ feeding post op.
- For MDT discussion and revision of the current SPK nutritional protocol.

[PP09]
RISK FACTORS FOR EARLY GRAFT FAILURE AFTER SOLITARY PANCREAS TRANSPLANTATION IN THE MODERN ERA: A SINGLE-CENTER, RETROSPECTIVE STUDY

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Objectives
Solitary pancreas transplantation (SPT, either pancreas after kidney (PAK) or pancreas transplant alone (PTA)) is performed less often than simultaneous pancreas kidney transplantation (SPK), and early graft loss is observed more frequently. Only very limited information exists on risk factors for early graft failure specific for SPT, especially in the modern era of improved immunosuppression and increased use of high-risk donor organs.

Methods
A single-center retrospective analysis was performed on all SPT in the Leiden University Medical Center since the introduction of modern induction immunosuppression (2000-2019). Short term outcome of SPT was compared to SPK. Multivariate regression analysis in the SPT group was performed to identify risk factors for pancreas graft failure in the first three months after transplantation.

Results
In total 50 SPT (40 PAK, 10 PTA) were analyzed and compared to 318 SPK. Three-month patient and death-censored graft survival was 100% and 70.0% in SPT and 98.1% and 92.1% in SPK, respectively (p=0.33 and p<0.001). Reasons for early graft loss in SPT transplants were thrombosis (80%), rejection (6.7%) and bleeding (6.7%). No association with immunologic factors was observed. Multivariate analysis in the SPT group showed that donor BMI (HR 1.43, p=0.02) and enteric drainage (HR 6.3, p=0.04) were associated with early graft loss.

Conclusions
SPT is associated with a higher risk for early graft loss than SPK. Possible risk factors include donor BMI and type of exocrine drainage. Early graft loss in SPT is mainly caused by thrombosis of the pancreas graft. Therefore, specific perioperative protocols for SPT should be developed with the aim of reducing pancreas graft thrombosis to improve outcome. The current analysis needs to be confirmed in larger multicenter analyses.

[PP10]
EXTRACELLULAR VESICLES FROM PATIENTS WITH DIABETIC NEPHROPATHY INDUCE ENDOTHELIAL

DYSFUNCTION THROUGH ICAM-1 AND VCAM-1 IN AN IN VITRO MODEL

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Objectives: Extracellular Vesicles (EVs) are membranous structures produced by cells which contain different cytoplasmic compounds and that have been described as potentially pathogenic elements in endothelial dysfunction (ED) through a modification of the expression of endothelial receptors. The mechanisms of ED in patients with chronic kidney disease (CKD) and diabetes mellitus (DM) are not well defined, although EVs could have a key role. The main objective was to analyze the potential induction of ED by EVs and its mechanisms in patients with DM and CKD.

Methods: cross-sectional study with sera from 11 patients with a mean age of 46±7.6 years (45% women) and CKD (eGFR 18±7 mL/min) due to diabetic nephropathy (DM1), grouped into 4 pools. The role of the EVs was studied in an *in vitro* model of ED with HMEC-1 cells exposed during 72 hours to supplemented medium with: a) patient sera (group 1/red), b) EVs-depleted patient sera (group 2/orange) and c) EVs-depleted control sera in which patient's EVs were added (group 3/yellow). Changes in the expression of vWF and the membrane adhesion receptors VCAM-1 and ICAM-1 were analyzed in the cells exposed to the different conditions, with respect to the healthy donor serum.

Results: the expression of ED markers (vWF, VCAM-1 and ICAM-1) in cells exposed to patient serum (with or without EVs) was higher compared to that observed after exposure to control sera (vWF, p <0.01; Fig. 1A; VCAM-1, p <0.01; Fig. 1B; ICAM-1, p <0.01; Fig. 1C). Moreover, EVs depletion significantly decreases the expression of VCAM-1 and ICAM- 1 with respect to the patient's serum (Fig. 1B, p <0.01 and 1C, p <0.01), but not vWF expression.

Conclusions: EVs increase endothelial damage through an increased VCAM-1 and ICAM-1 expression, both being inflammatory markers associated with leukocyte adhesion. Thus, EVs constitute a pathogenic element in ED in patients with DM1 and CKD.

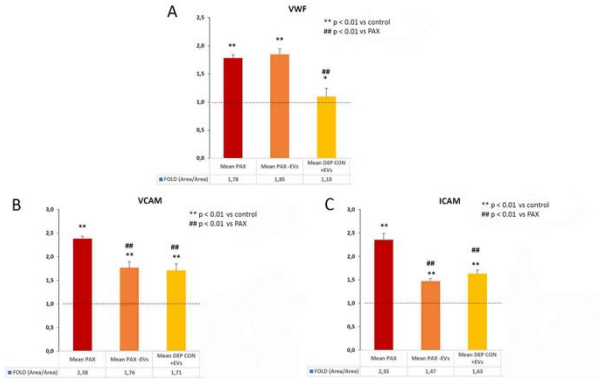

Figure 1