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ABSTRACT BOOK

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ORAL PRESENTATIONS

CLINICAL: ISLET

OP01

DEVELOPMENT OF AN ARTIFICIAL INTELLIGENCE MODEL TO SELECT DONORS FOR ISLET TRANSPLANTATION

Pierre Bauvin*[1], Ariane Courtinat[1], Violeta Raverdy[1], Pauline Petit[1], Delalleau Nathalie[1], Mehdi Maanaoui[1], Mikael Chetboun[1], Gmyr Valery[1], Julie Kerr-Conte[1], Francois Pattou[1]

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Background: Pancreatic islet transplantation (PIT) is an effective approach for the treatment of insulin-deficient diabetes. The metabolic benefits of PIT are dependent on the numbers of islets transplanted that survive engraftment. However, islet number varies widely between donors, due to highly heterogeneous characteristics impacting pancreas quality. Predicting the islet number from the donor characteristics remains challenging, but is crucial for pancreas selection. We aimed to develop a model using artificial intelligence (AI) to predict probability of exceeding 200,000 islets-equivalent (IEQ) after purification.

Methods: We used all islet samples undergoing isolation and purification, from 2003 to 2022 that were recorded in our database, to develop a model able to classify data as superior or inferior to 200,000 IEQ. We used internal-external validation with bootstrapping on the most recent 20% of the sample. We considered all donor characteristics at the time of the team's decision to accept the pancreas. We compared several AI approaches including decision trees, random forest, Xgboost, against an existing score for donor selection: the North American Islet Donor Score (NAIDS).

Results: Data from 844 donors were included in the analysis with 249 (29.5%) of them leading to more than 200,000 IEQ after purification. Five variables were consistently selected in the predictive models out of the 101-baseline donor features available: BMI, age, blood pressure, glycaemia, and cold ischemia. The different AI models resulted in similar performances, with accuracy ranging between 0.69 and 0.73 (versus 0.66 for NAIDS score), while using fewer attributes than the existing score. The decision tree approach has also enabled for a more interpretable model. Thus, the first and most discriminant branch of decision trees divided the data based on the BMI. The second branch separated patients by age (cut-off 56 years-old), and the following descendent branch distinguished high and low blood pressure.

Conclusions: Artificial intelligence approaches allow to select donors to maximize islet number after purification, from a small set of predictive variables. Its performance remains to be assessed in the context of external validation using prospective data collection.

OP02

IMPROVED PANCREATIC ISLET ISOLATION YIELD AFTER ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION OF CONTROLLED DONATION AFTER CIRCULATORY DEATH DONORS

Rutger van Rooden*[1], Jason Doppenberg[1], Madeleine van Dijk[1], Femke de Goeij[2], Fenna van der Heijden[2], Ian Alwayn[1], Eelco de Koning[3], Jeroen de Jonge[2], Marten Engelse[3], Volkert Huurman[1]
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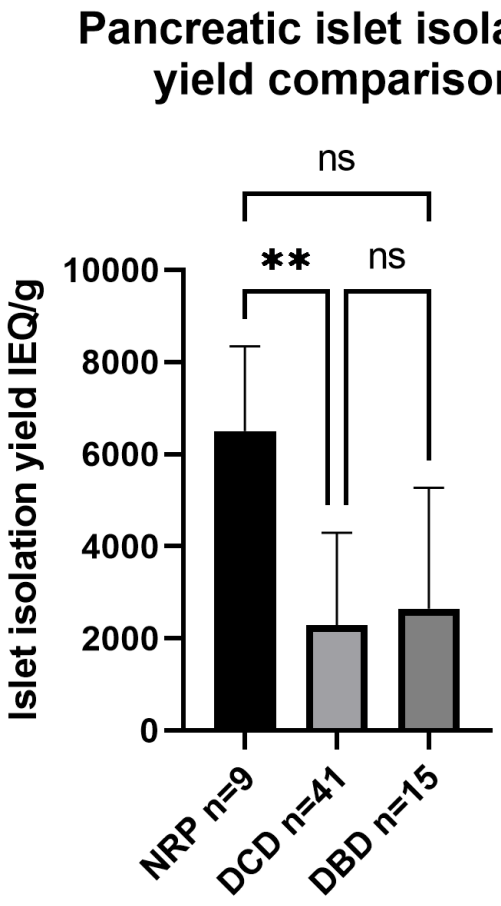
Background: Shortage of suitable donor organs has led to increasing interest in abdominal Normothermic Regional Perfusion (aNRP). This is an in-situ normothermic oxygenated donor perfusion technique that can be used prior to procurement during controlled Donation after Circulatory Death (cDCD) procedures. It allows organ evaluation and potentially improves transplantation outcomes. There are few data on the effect of aNRP on pancreatic islet isolation outcome. Our aim is to evaluate the impact of aNRP on extended criteria pancreatic islet isolation outcomes.
Methods: A retrospective analysis was performed on pancreatic islet isolation outcomes from cDCD+aNRP (n=9), regular cDCD (n=41) and Donation after Brainstem Death (DBD, n=15) pancreata. These isolations were performed using a standardized procedure on comparable, matched for donor age (60-75), donor pancreata, see table 1. Islet isolation outcome was expressed in Islet Equivalent (IEQ) per gram pancreas weight. To assess pancreatic islet function, a dynamic Glucose Stimulated Insulin Secretion (dGSIS) test was performed. Islet survival was assessed by calculating the ratio between the change in IEQ of day 0 and day 1.
Results: Donor baseline characteristics were not different between groups. Isolations from cDCD+aNRP pancreata yielded more islets (6500±2607) compared to cDCD (2285±1455, p<0.01) or DBD (2646±1681, p=0.14) pancreata (see Figure 1). The islet survival rate after culture was also higher for the cDCD+aNRP islets (96%±21.8%) compared to cDCD (75%±15.3%, p=0.82) and DBD (77%±19.8%, p=0.41) islets, although this difference was not significant. dGSIS tests in 5 cDCD+aNRP islet preparations showed a mean stimulation index of 4.48, indicating good functionality.
Conclusions: aNRP may lead to higher islet yield after an islet isolation procedure of a cDCD pancreas, the islets were viable and showed good functionality. aNRP could increase utilization of islet preparations that can be used for islet transplantation.

Table 1 – Comparison of donor characteristics between groups.

Donor characteristics					
	cDCD+aNRP (n=9)	cDCD (n=41)	p-value	DBD (n=15)	p-value
Age (years)	72	65	0.97	66	0.99
Sex (% male)	60%	70%	0.48	50%	0.69
Height (cm)	175	174	>0.99	172	>0.99
BMI (kg/m^2)	23.5	25.0	0.55	27.0	0.26
Amylase (U/l)	86.5	69.0	0.87	78.0	>0.99
Pancreas mass (g)	79.7	90.4	>0.99	82.0	>0.99
CIT (hours:min)	12:18	9:11	0.98	10:42	0.90

Figure 1- Comparison of pancreatic islet isolation yield per group.



OP03

INSULIN THERAPY AND WEIGHT GAIN IN TYPE 1 DIABETES (T1D): WHAT CAN WE LEARN FROM ISLET TRANSPLANTATION?

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Background: Weight gain in T1D patients has become a clinical problem due to less strict diets and more stringent glycemic targets. Thus, the number of overweight T1D in the USA increased from 3.4% in 1988 to 22.7% in 2007. Hyperinsulinism is involved in the genesis of obesity but in T1D, the impact of insulin therapy in weight gain is not established. Islet transplantation, now reimbursed, makes it possible to interrupt insulin. The aim of this work was to study weight evolution in an islet-transplanted population after obtention of insulin-independence and to determine the weight predictive factors.

Methods: monocentric retrospective study comparing the evolution of anthropometric and metabolic parameters before and 1, 3, 5 and 10 years after islet transplantation alone performed between 2003 and 2017, in 41 patients.
Results: The population (21 women, 20 men), age (median (IQR)) 48 (42-55) years, had a weight of 71.4 (66-78) kg, a BMI of 24.7 (22.9-26) kg/m2, a body fat percentage (DEXA) of 26.3 (20-31.5) %, and a daily insulin requirement of 41.3 (30.5-47) U/d. The median weight loss at 1, 3, 5 and 10 years was 6.6 (p=0.003), 4.9 (p=0.007), 5.0 (p=0.043), and 5.4 kg (p=0.418) respectively, and correlated with the decrease in insulin doses (r^2=0.295; p=0.0005) at 5 years. In the 18/41 patients with a pre-transplantation BMI >25 kg/m², 10-year weight loss was permanent, unlike in the 23/41 patients with pre-transplantation normal BMI. The glycemic balance was identical between the 2 groups.
Conclusions: A weight loss is observed with islet transplantation, more marked in initially overweight subjects and correlated with the insulin dose decrease. These results suggest a role of exogenous insulin therapy in the weight gain of T1D patients, that is likely to limit their access to the islet transplant. The latter, however, could be modulated by the level of insulin-sensitivity.

OP04

ISLETSWIPE: THE PLATFORM VALIDATION BY THREE INDEPENDENT CENTRES.

David Habart*[1], Martin Capek[2], Valecka Jan[3], Adam Koza[4], Jan Kubant[5], Ivan Leontovyc[1], Bass Brinkhof[6], Dirk-Jan Cornelissen[6], Zuzana Berkova[1], Lucie Kosinova[1], Jan Kriz[1], Katerina Bittenglova[1], Klara Zacharovova[1], Nicholas Magrane[7], Alena Habartova[8], Sarah Suergiu[9], Frantisek Saudek[1]
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Background: For clinical islets transplantation, we previously developed a web service IsletNet to automatically assess microscopic images of isolated islets. Deep learning technology requires training annotations (contours of islets and exocrine tissue). Annotating the embedded and adjacent islets represents a particular challenge. The expert consensus remains unknown due to the lack of a graphical tool for opinion exchange. For this reason, we developed a mobile application, IsletSwipe.
Methods: In this validation study, experts annotated shared images of 67 islets using IsletSwipe by drawing with finger tip, rubber pen, or stylus on cell phone screen. Expert lines were trimmed and analyzed in Fiji using specifically designed macros. To determine the drawing precision, experts were asked to trace the red template line (RTL) separating adjacent islets (Fig 1A) or the red islet contour (RIC, Fig 2A, grey background). The average distance between the expert line and RTL was calculated; good precision if ≤ 2 pixels (Fig 1B, pink strip). Expert contour and RIC were used to

calculate islet volumes which were then compared (Fig 2B, pink strip). Next, the experts annotated 47 dithizone stained embedded or adjacent islets.
Results: Initially, 2 of 11 experts failed to achieve the precision required for IsletNet training (Fig 1B, experts 7,8). When the same experts used the stylus, they reached a good precision (Fig 2B, A,B,C,D). The volumes of 6 embedded islets of different size categories demonstrate the spread of opinions among experts (Fig 2B, small islets 4,6,9 and large islets 2,5,20; Fig 2A bottom).
Conclusions: IsletSwipe supports rapid and precise islet contour drawing after a brief introduction. It provides for the first time the platform for generating expert consensus on the challenging islet contours. More experts are welcome to voice their opinions by drawing or by simply voting with IsletSwipe. This can potentially help standardize islet counting.
Support: Czech Health Research Council, grant NU22-01-00141

Fig 1A:

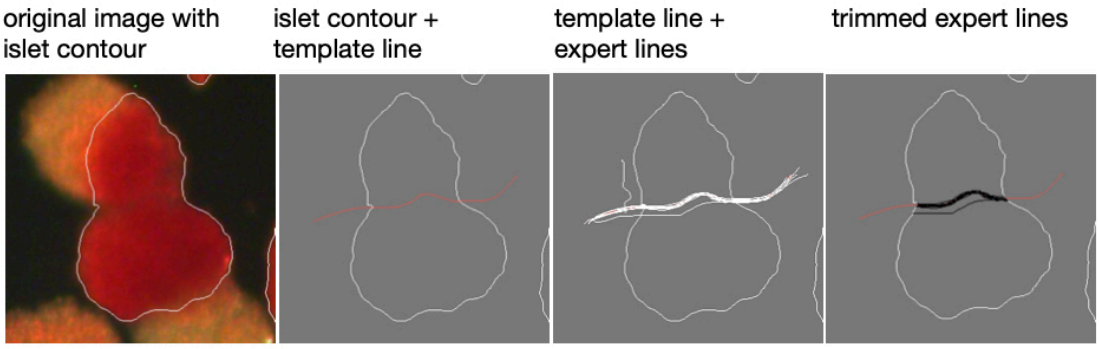

original image with islet contour
islet contour + template line
template line + expert lines
trimmed expert lines

Fig 1B

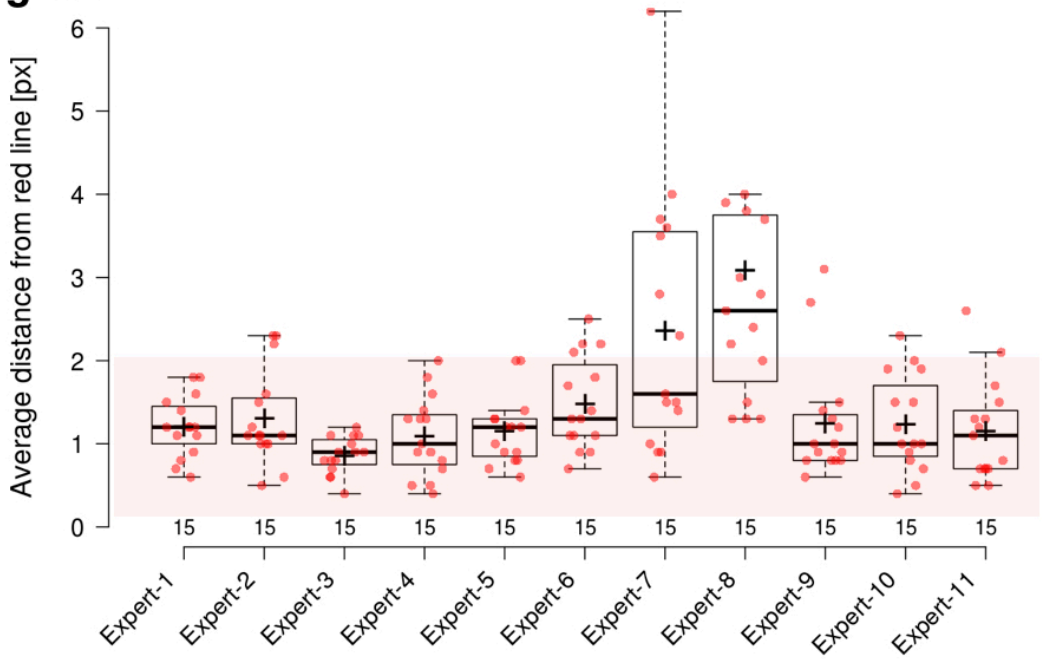
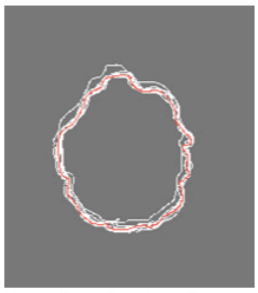
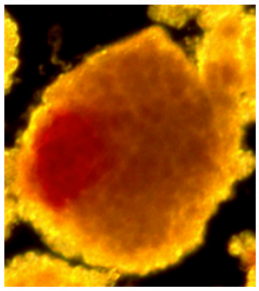

Average distance from red line [px]
0
1
2
3
4
5
6
15
15
15
15
15
15
15
15
15
15
15
Expert-1
Expert-2
Expert-3
Expert-4
Expert-5
Expert-6
Expert-7
Expert-8
Expert-9
Expert-10
Expert-11

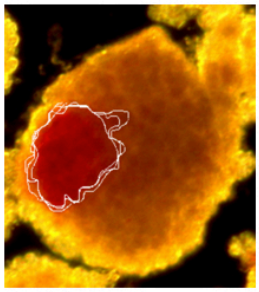
Fig 2A



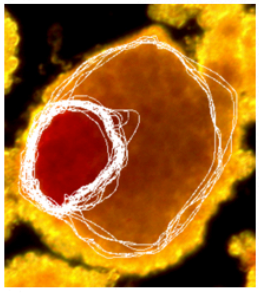
Control A: drawing precision



Islet-19, original image

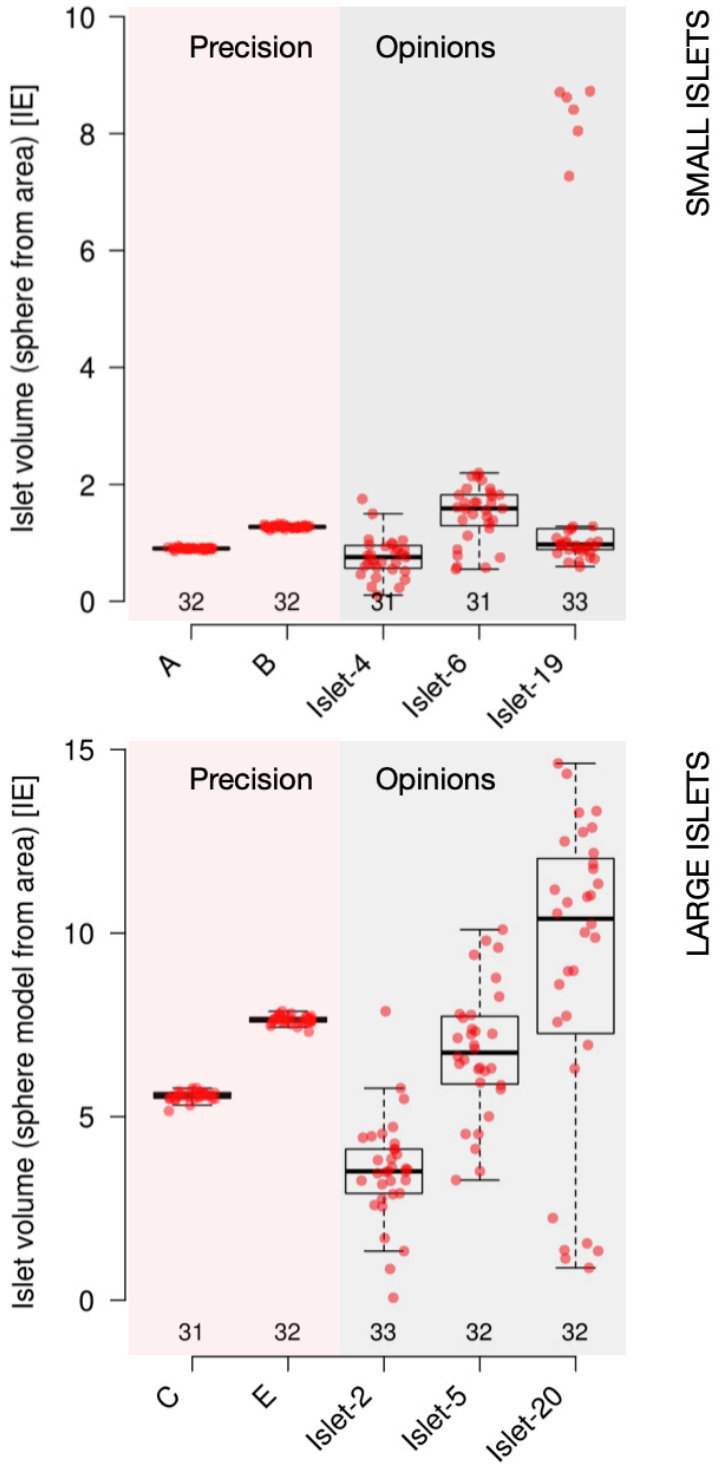


Repeatability of expert-6



Range of expert opinions

Fig 2B



OP05

TNF-A BLOCKADE IN IMMUNOSUPPRESSED ISLET TRANSPLANT RECIPIENTS - A STUDY ON IN VITRO, CLINICAL AND CITR-DERIVED DATA

Cyril Landstra*[1], Merel Ruissen[1], Michiel Nijhoff[1], Maarten Tol[1], Francoise Carlotti[1], Marten Engelse[1], Eelco de Koning[1]

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Background: TNF-α blockade is widely used in peri-transplantation strategies. Most data showing improved graft outcome are from islet transplantation alone patients, who do not use immunosuppression (IS) at the time of islet transplantation (ITx). We hypothesize that Itx recipients that already use IS, e.g. islet-after-kidney, may benefit less from TNF-α blockade.

Methods: We extracted data from the CITR database on Itx recipients with and without etanercept, analyses are currently being performed. We also performed *in vitro* experiments and gathered additional clinical data on Itx recipients in our centre. TNF-α response of circulating mononuclear cells was measured *in vitro* after infusion of allogeneic islets in whole blood from patients with IS and healthy controls during 360 minutes, and compared to a control where culture medium without islets was added. Using a pre-post implementation strategy, clinical graft outcome was compared between Itx recipients that had received etanercept during their second Itx and a control group that had not, between 2010-2017. Beta score indicating graft function was assessed before and 3 months after Itx.

Results: TNF-α response significantly increased when blood from controls (n=9) was exposed to islets (TNF-α AUC 9057±3202 pg/360 min [islets] *vs* 5992±2118 pg/360 min [control medium]; p=0.010). This response to both islets and control medium was significantly higher (p=0.012 and p=0.020, resp.) compared to that in patients with IS (n=8), where TNF-α was lower and did not increase significantly (AUC 5470±2446 pg/360 [islets] *vs* 2131±953 pg/360 min [control medium]; p=0.27). In Itx recipients that were treated with etanercept (n=7) compared to those who were not (n=9), baseline characteristics including maximum C-peptide and number of islets infused were similar. Beta score increased from 3.1±1.7 – 4.3±2.7 (p=0.23) in etanercept and from 3.6±2.1 – 6.3±1.9 (p=0.052) in controls, with no difference between post-Tx beta score (p=0.18). Results of the CITR-derived data will be presented at the conference.

Conclusions: Peri-transplant etanercept treatment seems to have an attenuated effect on islet graft outcome in previously immunosuppressed patients, which may be due to a mitigated TNF-α response. Confirmation of these findings using the large CITR registry will follow.

OP06

WHAT DO PATIENTS WANT FROM BETA CELL REPLACEMENT DEVICES?

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Background: Beta cell delivery devices can potentially improve clinical outcomes of beta cell replacement therapy. Despite the progress in developing new devices, little is known about patient preferences regarding the application of islet delivery devices. Literature suggests that patients prefer small devices with females emphasizing visibility, but the relation between preferences, diabetes distress, or expected improvement is not well known. We report on a survey done amongst > 800 patients and caretakers or parents regarding their expectations concerning delivery devices.
Methods: Patients were invited to fill out a web-based questionnaire (Qualtrics) to evaluate their preferences for delivery devices, concerning device dimensions, device characteristics, minimal function and duration and preferred implant sites. Included parameters were age, gender, and diabetes history, including years since diagnosis, self-reported recent time in range, self-reported recent hemoglobin A1c (HbA1c), diabetes-related distress, type of treatment center, and current treatment. We evaluated answers of 852 respondents (age: 16 – 30 years (N=154), 30 – 50 years (N=310), 50 – 70 years (N=303), >70 years (N=38), and parents/caretakers (N=47); gender: male (N=356), female (N=495))
Results: Device dimensions were considered irrelevant by 31% of respondents. Implantation of multiple devices 5.1 ± 2.9, is acceptable. 12 months between two implantations is accepted by 58% of the respondents. Time between repeated implantations was considered more important than device dimensions, or multiple devices simultaneously (P<0.0001). Compared to patients, parents/caretakers prefer fewer devices simultaneously (χ^2 (1, N=180) = 5.41; P=0.02), longer minimum retransplantation interval (χ^2 (1, N=127) = 4.119; P=0.04), and had less interest in an islet delivery device to treat type 1 diabetes (χ^2 (1, N=268) = 8.04; P=0.005).
Conclusions: Based on the collected responses, devices should not require additional daily interventions. Minimum replacement interval of 12 months is preferred to minimize the impact due to frequent hospital visits and 24 months for children. Transplanting multiple devices is in general accepted, although one should consider the potential discomfort while performing daily activities.

CLINICAL: PANCREAS

OP07

DYNAMIC CONTRAST-ENHANCED ULTRASOUND (DCEUS) IN PANCREATIC TRANSPLANTATION: NORMAL VALUES AND ITS POTENTIAL UTILITY IN EVALUATING REJECTION.

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Background: Dynamic contrast-enhanced ultrasound(dCEUS) is a novel non-invasive ultrasonographic technique that allows the quantification of tissue capillary perfusion.

This study aims to determine dCEUS values in normofunctioning pancreatic grafts and their potential utility in assessing rejection.
Methods: Prospective study including all pancreas transplantations performed in our centre between October 2016 and January 2020. These pancreatic grafts were evaluated by dCEUS at 1 week, 3 weeks and 12 months after surgery. A protocol biopsy was performed immediately after dCEUS evaluation in the 3 weeks and 12 months evaluation. In addition, a dCEUS was also performed in all pancreatic graft biopsies performed in this period (dysfunction or surveillance following treatment for rejection), regardless of the transplant date. Patients with postoperative complications were excluded. VueBox® software was used to evaluate time-intensity curves of each dCEUS, providing 12 parameters of each. Evaluations were classified according to the biopsy in normal and rejection group and compared between them. Those without biopsy were classified according to the clinical management. Using Youden's criteria, cut-off values were determined for all the evaluated parameters.
Results: During this period, 132 dCEUS studies and 85 biopsies were performed in 56 patients. Three patients were excluded because of postoperative complications (5 studies). Time-intensity curves showed a high dispersion of the values of all evaluated parameters during the first 3 months, which may be related to postsurgical factors. After this period, significant differences were only observed in parameters dependent on the area under the curve (median [IQR], a.u.), with lower enhancement in the presence of rejection (wash-in AUC: 1589 [1704] rejection vs 3386 [5568] normal, p=0.007). In patients with concomitant biopsy, a cut-off value of 601 for peak enhancement and 118 for wash-in rate were found (AUC 0.64 [0.53-0.76, 95%CI], p=0.026 for both).
Conclusions: Acute graft rejection after the first 3 months is associated with a lower graft perfusion when evaluated by dCEUS. These results highlight that dCEUS may be a useful non-invasive tool to screen patients requiring pancreas graft biopsy or aid in the diagnosis of pancreas graft rejection.

OP08

EXPERIENCE OF 105 PANCREAS RETRANSPLANTS AND PREDICTORS OF OUTCOME

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Background: Pancreas retransplantation(PRT) activity has declined in recent years mirroring the tendency of overall numbers of pancreas transplantation(PT). This study aimed to analyze our experience with PRT over a 25-year program searching for reliable predictors of outcome.
Methods: Donor and recipient characteristics and outcomes data were retrospectively gathered from our databank. An in-depth analysis of PRT and previous PT was performed. Sensitization was considered either if an increase of 20% in cPRA occurred or by appearance of anti-DQs after the primary PT.
From November/2000 to september/2022, 1,133 PT were performed, being 105 PRT(9.3%). PRT categories included Re-PAK in 92(88%) and Re-PTA in 13(12%) cases. Cause of primary graft loss(CPGL) was technical in 43(41%), immunological in 58(55%) and other in 4(4%). Timing of previous graft loss was early(< 3 months) in 52(49%) and late in 53(51%). The mean time interval from primary PT to PRT was 32.5 months(4-241) being significantly lower whether CPGL was technical compared to

immunological(22.1 x 81.3 months, p<0.001). The need of primary graft transplantectomy before or during PRT differed significantly being 100% for technical CPGL and 38% for immunological CPGL(p<0.001). 1-year patient survival was similar between PRT and a control cohort of 365 primary solitary PT(91.2% x 92.1%,p=0.83) and also was 1-year pancreas graft survival(69.2% x 72.9%, p=0.51). 1-year patient survival for PRT was also similar according to technical or immunological CPGL(92.5% x 89.4%,p=0.72). There was a tendency of higher pancreas graft survival after PRT for technical vs immunological CPGL(72.5% x 66%, p=0.64). When subcategorized the group with immunological CPGL for early(< 5 years) and late(>5 years) immunological loss, there was a tendency of higher 1-year pancreas graft survival for the latter(84.6%) compared to technical (72.5%) or early immunological CPGL(58.8%, p=0.20).Sensitization after primary PT determined inferior 1-year pancreas graft survival in PRT compared to non-sensitized patients(44.4% x 79.7%, p=0.002).
Conclusions: PRT has achieved similar patient and pancreas graft survivals to primary solitary PT in selected groups. Early immunological CPGL and sensitization may represent a predictor of inferior outcome after PRT.

OP09

PREDISPOSING FACTORS TO MAJOR ADVERSE CARDIOVASCULAR EVENTS FOLLOWING SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

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Background: Cardiovascular disease (CVD) is one of the leading causes of death in chronic kidney disease and type 1 diabetes patients. Although simultaneous pancreas-kidney transplant (SPKT) improves survival, CVD is still a major determinant of morbidity and mortality in these patients. The aim of this study was to assess the incidence and evaluate risk factors of major adverse cardiovascular events (MACE) in SPKT recipients with both functioning allografts.
Methods: We undertook a retrospective, population-cohort study of every SPKT performed in our center between January 1st 2000 and December 31st 2020, with a follow-up period of at least 12 months. Of the 254 transplant patients evaluated, 212 were included and stratified according to the presence of a MACE in the post-transplantation period. MACE was defined as myocardial infarction, new congestive heart failure, percutaneous coronary intervention, stroke and peripheral vascular disease requiring surgical intervention.
Results: A total of 49 (23%) patients suffered a MACE after SPKT. These patients were older (p=0.002) and with longer DM disease (p=0.009) compared with the group without MACE. The remaining demographic and clinical features were similar between groups. The overall incidence rate of MACE was 3.13 (95% CI 2.42-4.06) events per 100 person-years and was almost 4 times higher (p<0.001) in patients with a pretransplant MACE compared to those without previous events. Coronary heart disease and peripheral arterial disease incidence rates were 11 (p<0.001) and 4.5

(p<0.001) higher, respectively, in SPKT recipients with a pretransplant MACE. More than 25years of diabetes (p=0.048), use of prednisolone (p=0.047) and a pre-transplant MACE(p<0.001) were independent predictors of overall MACE after SPKT.
Conclusions: Our study shows that simultaneous pancreas-kidney transplant patients are at high risk of suffering cardiovascular events. MACE pre-transplant, diabetes duration and the use of corticosteroids strongly correlate to MACE after transplantation. Therefore pre-existing vascular disease should be given great emphasis during recipient selection for SPKT and CVD factors should be rigorously managed.

OP10

PROGRESSION OF DIABETIC RETINOPATHY AFTER PANCREAS AND KIDNEY TRANSPLANTATION IN A PROSPECTIVE RANDOMIZED TRIAL COMPARING EVEROLIMUS VERSUS MYCOPHENOLATE

Barbora Hagerf (Voglová)*[1], Lenka Nemetova[1], Zuzana Hladikova[1], Martina Zahradnická[1], Katerina Kesslerová[2], Tomas Sosna[2], Kvetoslav Lipár[3], Peter Girman[1], František Saudek[1]
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Background: Successful pancreas and kidney transplantation (SPK) in type 1 diabetic (T1D) patients does not initially halt progression of diabetic retinopathy (DR), but tends to stabilize it in the long run. mTOR inhibitors are known for their antiangiogenic effect, but the impact of long-term systemic immunosuppression on DR had not yet been prospectively studied. We initiated a prospective randomized trial comparing the effect of either everolimus (E) or mycophenolic acid (MPA) on the course of DR in SPK recipients. (EUDRACT No.2013-004934-14)
Methods: Waitlisted Type-1 diabetic subjects were randomized to treatment with MPA or E together with tacrolimus, 6 weeks steroids and ATG induction. Eye examination including optical coherence tomography was done at the baseline, 6, 12 and 24 months. The composite primary endpoint comprised new need for laser therapy, newly diagnosed proliferation, clinically significant macular edema (CSME), best corrected visual acuity (BCVA) worsening. For statistical evaluation we used t-test, Mann-Whitney test, Fisher's exact test, Kaplan-Meier test and log-rank test. Endpoints were evaluated per patient and per eye.
Results: Out of 64 enrolled patients, 54 (MPA 29, E 25) completed the follow-up. Most of these had proliferative DR (82% eyes in MPA and 78% in E group) with previous laser treatment. 2-year patient and death-censored pancreas and kidney graft survival rates did not differ between the groups. 59% of the patients in the MPA group and 40% in E group met the primary endpoint (p=0.3), mostly due to new need for laser treatment and visual acuity worsening. When analyzed per eye, the need for laser therapy was more frequent in the MPA group, reaching statistical significance in the second year post-transplant (24.5% vs 8.2% eyes, p=0.04), which corresponded with BCVA worsening (29.8% and 12.2%, p=0.03). Retinopathy-related BCVA worsening was significantly higher in the MPA than E group. (21% vs 6.1%, p=0.047). There was no case of new blindness. Central retinal thickness increased in the 6th month post-

transplant in both groups with subsequent restoration at 12 and 24 months. CSME rate was similar in groups (MPA 10.3%, E 8%, p=0.99).
Conclusions: We observed retinopathy progression in both groups, with slightly more favorable outcomes in the everolimus-treated group.

OP11

REFERRAL PRACTICES AND RECIPIENT OUTCOMES OF RECIPIENTS WITH TYPE 2 DIABETES MELLITUS UNDERGOING SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANT

Ruth Owen*[1], Harry Carr[2], Claire Counter[3], Emily Thompson[1], Derek Manas[1;3], James Shaw[1;4], Colin Wilson[1;4], Steve White[1;4]
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Background: 90% of the UK diabetic population are classified as T2DM. This study aims to compare outcomes after SPKT between recipients with T1DM or T2DM.
Methods: Data on all UK SPKT's from 2003-2019 were obtained from the NHSBT Registry (n=2,236). Current SPKT selection criteria for T2DM requires insulin treatment and recipient BMI<30kg/m2. After exclusions (re-transplants/ambiguous type of diabetes) we had a cohort of n=2,154. Graft and patient survival analyses were conducted using Kaplan-Meier plots and Cox-regression models. Complications were compared using chi-squared analyses.
Results: 95.6% of SPKT's were performed in recipients with T1DM (n=2,060), and 3.4% (n=94) in T2DM. Univariate analysis showed comparable outcomes for pancreas graft survival at 1yr (p=0.120), 3yrs (p=0.237), and 10yrs (0.196) and kidney graft survival at 1yr (p=0.438), 3yrs (p=0.548), and 10yrs (0.947). Patient survival was comparable at 1yr (p=0.886) and 3yrs (0.237) and at 10yrs (0.161). Multi-variate analysis showed comparable outcomes in pancreas graft survival (p=0.564, HR 1.221, 95%CI 0.619, 2.406) and patient survival (p=0.556, HR 1.280, 95%CI 0.563, 2.911). Comparable rates of common complications were demonstrated. Despite these results and similar results from other studies the percentage of SPKTs performed in recipients with T2DM in the UK is well below that of our American and European counterparts.
Conclusions: This is the largest series outside of the US evaluating outcomes after SPKT and shows similar outcomes between T1DM and T2DM recipients. It is hoped dissemination of this data will lead to increased referral rates and assessment of T2DM patients, with end stage renal failure, who could benefit from SPK transplantation.

OP12

A PROSPECTIVE STUDY OF DONOR-SPECIFIC ANTI-HLA ANTIBODY MONITORING IN PANCREAS TRANSPLANTATION

Ana Claudia Vidigal[1], Marcelo Perosa*[1], Fernanda Danziere[1], Renato De Marco[2], Adriana Bruscato Bortoluzzo[3], Maria Kelly Venezuela[3]
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Few studies have evaluated the role of donor-specific antibodies(DSA) in pancreas transplant(PT).The aim of this study was to analyze the incidence of DSA pre and post-PT and outcomes in a protocol of routine DSA monitoring.
From March/2018 to December/2021 234 technical successful PT, being 135 SPK and 99 solitary PT(S-PT) of which 86 PAK and 13 PTA were followed for detection of posttransplant(PO) DSA. All PT received induction therapy with Thymoglobulin, tacrolimus, mycophenolate sodic and steroids. Screening of HLA-antibodies was performed by Luminex at 3, 6 and 12 months PO or when a rejection episode occurred and twice a year thereafter for all S-PT. Any DSA with MFI>500 was registered. All kidney or pancreas rejection was biopsy-proven and stained for C4d.
The prevalence of *de novo* DSA was significantly higher among S-PT, 19(19%),compared to SPK recipients 12(8.9%),*p=0.03*,OR=2.43. The average time of DSA appearance was 6.4 months(3-28) and most of them, 25(80.6%),were triggered after a rejection episode. Overall, more rejection episodes occurred in patients with DSA+ than in DSA-(80.6%x24.1%,*p<0.001*,OR=13.1).Among SPK patients, DSA+ showed a higher rate of kidney immunological loss(16.7%x1.6%,*p=0.03*,OR=12.1),but similar pancreas immunological loss and kidney, pancreas and patient survival. Among DSA+ S-PT patients, rejection occurred in 16(84.2%),being 12(63.2%) confirmed or suspected antibody-mediated rejection(AMR). The presence of C4d+ in pancreas biopsies was higher in DSA+ S-PT(36.8%x11.3%,*p=0.01*,OR=4.6) as was the rate of immunological graft loss(42.1%x8.7%,*p=0.001*,OR=7.6) with inferior 1-y(68.4% x 96.2,*p=0.001*,OR=0.08) and long-term(57.9%x91.2%,*p=0.001*,OR=0.13) pancreas survival. Interestingly, long-term pancreas survival among S-PT patients was comparable between "weak"DSA+(MFI<1500) and DSA-(83.3%x91.3%,respectively)which were significantly higher than DSA+(MFI>1500) S-PT(46.2%,*p<0.001*) patients.
Occurrence of PO DSA was higher in S-PT than in SPK recipients.*De novo* DSA was strongly related to higher rate of rejection, AMR, C4d+ pancreatic biopsies, immunological graft failure and inferior pancreas survival,particularly if MFI>1500. A protocol of routine DSA monitoring could improve diagnosis and interventioning for immunological events after PT.

BASIC SCIENCE: ISLET & PANCREAS

OP13

INHIBITION OF TISSUE FACTOR EXPRESSION IN ISLETS GRAFT USING A SYNTHETIC SIRNA

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Background: The intensity of IBMIR (Instant Blood-Mediated Inflammatory Reaction) depends on the amount of tissue factor (TF) molecules on the islet cells. At the same time, TF is an important growth factor stimulating islet graft revascularization. To reduce the intensity of IBMIR and to improve the early function of islet graft, we tested the possibility of the short-term inhibition of TF synthesis in islet cells using RNA interference.
Methods: Male Brown Norway rats (250-270g) served both as pancreatic islet (PI) donors and recipients. PI were isolated using collagenase digestion according to standard protocol. After overnight cultivation PIs were transfected with anti-TF siRNA (s130189, ThermoFisher Scientific, USA) using lipofection (Lipofectamine RNAiMAX, 50nM; n=6) or microporation (Neon, 2 pulses, 950 V, 20 ms, 200 nM; n=6). After 24 hours, treated PIs were transplanted to portal vein of streptozotocin diabetic animals in marginal dose (2 PI/g).
Results: Both methods led to a comparable decrease in TF mRNA expression - microporation of siRNA reduced the amount of TF mRNA by 76/55%, lipofection by 75/70% after 24/48 hours, respectively. Both methods led to a significant decrease in TF protein expression as proven by western blot and a significant reduction of liver ischemia after PI transplantation as proven by MRI. PIs normalized glycemia of all recipients transplanted with lipofected PIs but none with microporated PIs.
Conclusions: AntiTF-siRNA transfected by microporation efficiently reduced the amount of TF for 24 and 48 hours but did not improve the function of transplanted PIs. AntiTF-siRNA transfected by lipofection efficiently reduced amount of TF for 24 hours and significantly improved the function of transplanted PIs. Microporation likely caused the Off-target effect in PI graft.
Acknowledgment: Funded by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Pr. EXCELES, No. LX22NPO5104) - The Next Generation EU.

OP14

NUTRIENT CONTROL OF INSULIN SECRETION IN STEM CELL-DERIVED ISLETS

Chencheng Wang*[1;2], Aleksandra Sizenshtadt[2], Shadab Abadpour[1;2], Andrea Dalmao Fernandez[3], Merete Høyem[1], Justyna Stokowiec[2], Petter Angell Olsen[2;4], Simona Chera[5], Luiza Ghila[5], Helge Ræder[5;6], Stefan Krauss[2;4], Hanne Scholz[1;2;7;8]

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Background: Stem cell-derived islets (SC-islets) are unlimited human beta cell sources for transplantation. Here, we optimized an SC-islets differentiation protocol, investigated its efficiency, and performed a systematic study on the different nutrients that controlled insulin secretion (IS) in these SC-islets.

Methods: Insulin-positive cells (IPCs) differentiation protocol were optimized by the WNT signalling manipulation during stage 1 and 2. The differentiation efficiency was evaluated by flow cytometry. Static or dynamic IS stimulation of the SC-islets derived from the optimized protocol in response to different nutrient sources, including glucose, amino acid, and pyruvate, was investigated. The oxygen consumption rate (OCR) of SC-islets in response to glucose was evaluated by the Seahorse. Finally, SC-islets derived from the optimized protocol were transplanted in mice under the kidney capsule.
Results: Our data showed that the WNT inhibition at stage 2 significantly increased the pancreatic progenitor cells (XH001 cell line, P<0.001) and IPCs (XH001 cell line, P<0.01) differentiation efficiency than non-WNT inhibition. SC-islets can maintain GSIS ability for 4 weeks in vitro with an average secretion index (SI) of 1.45, and the SI significantly decreased to 1.12 in week 6 compared to week 2. Dynamic profusion showed that SC-islets have a biphasic IS in response to glucose and a monophasic IS in response to pyruvate. Amino acid alone cannot significantly stimulate IS. The OCR analysis shows SC-islets have a similar oxygen consumption pattern to human islets. 600 SC-islets were transplanted under the mice's kidney capsule. The human c-peptide was detectable 15 days post-transplantation and increased above 500 pM in 3/3 transplanted mice at day 31. In addition, these SC-islets prevented alloxan-induced diabetes in 3/3 of mice.
Conclusions: The IPCs' differentiation efficiency in this study was ensured through an optimized planar differentiation protocol. The SC-islets showed a 100% success rate in protecting the transplanted mice from alloxan-induced diabetes. In addition, the SC-islets' IS dependent on different nutrient sources was systematically characterized in this study. SC-islets in response to fatty acid and their nutrient dependency will be analysed in follow up studies.

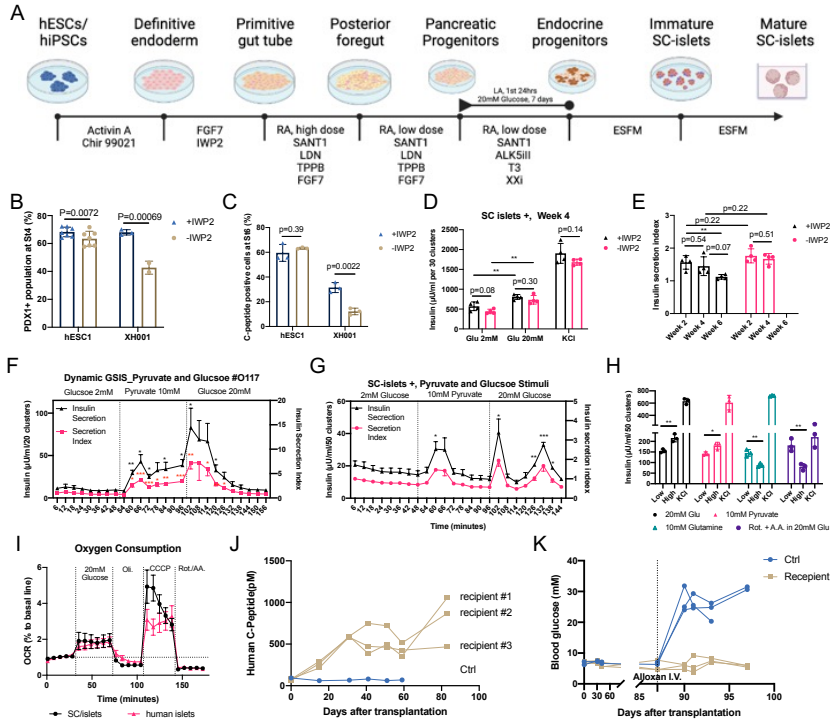

Figure: Nutrient control of insulin secretion in stem cell-derived islets.

(**A**) Schematic of the protocol for generating SC-islets.

(**B**) WNT inhibition at stage 2 increased the PDX1-positive cell population at stage 4 in the studied iPSC line.

(**C**) WNT inhibition at stage 2 increased C-peptide-positive cell population at stage 6 in the studied iPSC line.

(**D**) GSIS evaluation of SC-islets maintained *in vitro* at the fourth week of stage 6.

(**E**) Insulin secretion index of SC-islets maintained *in vitro* from week 2 to 6 at stage 6.

(**F**) Primary human islets' dynamic perfusion with pyruvate and glucose.

(**G**) SC-islets' dynamic perfusion with pyruvate and glucose.

(**H**) Different nutrient sources stimulated insulin secretion in SC-islets.

(**I**)Oxygen consumption measurement of SC-islets and primary human islets.

(**J**) Human C-peptide measurement of transplantation study.

(**K**)Blood glucose measurement of transplantation study.

OP15

OPEN THIN FILM MICROWELL BETA CELL DELIVERY DEVICES FOR TYPE 1 DIABETES

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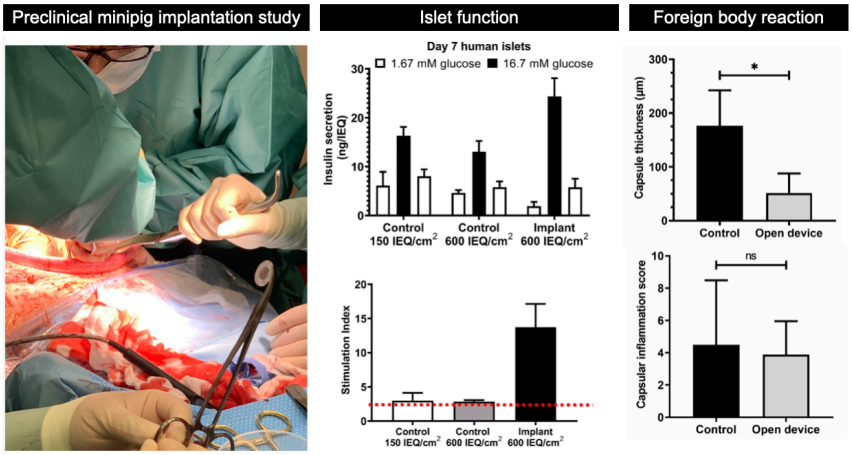
Background: In the last decade new developments in beta cell replacement have led to significant improvements in the generation of stem cell islets in treatment of type 1 diabetes. Beta cell delivery devices are needed to deliver these cells at the most optimal location. Traditionally most research focussed on closed immunoprotective devices, recently there is more interest in the use of retrievable open delivery devices. We developed an open thin film microwell delivery device for islets and beta cells from a specifically selected clinically used biomaterial.

Methods: Devices are made from thin ~50µm polyvinylidene fluoride films with a predefined pattern of pores and array of equally shaped microwells. Microwell dimensions are designed to capture minimally one islet per well separating them while controlling their distribution. The pores enable revascularization throughout the delivery device. Devices consists of a microwell bottom closed with a microporous lid separated by a support ring. We developed a tailormade cell seeding method reproducibly uniformly distribute islets in the delivery device

Results: Primary human, or rat islets in mouse- and rat-sized implants showed similar, or improved viability and function, compared to controls after 7 days of *in vitro* culture. We further optimized the cell loading capacity of our devices based on computational modeling and *in vitro* studies to increase the cell loading capacity without negatively affecting oxygen levels. Interestingly, the most important factor which negatively affects oxygen supply to islets is their size, but not the distance in between. Subcutaneous implantation in rats according to ISO 10993 standards revealed delivery devices become well vascularized and elicit a minor foreign body response over a 3-month period. We successfully implanted and retrieved these devices at 5 different locations in a preclinical mini pig model and determined the most optimal transplant site for future functional studies is either the intramuscular or preperitoneal site.

Conclusions: We were able to design and manufacture a scalable open beta cell delivery device which can support islet function and survival. Implantation studies revealed that the devices elicit a minor foreign body response and show good vascularization throughout the device after 3 months.



From left to right: impression of minipig implantation study, human donor islet function in delivery devices, and quantification of foreign body reaction after a 3-month subcutaneous implant study.

OP16

PUMP-LESS MICROFLUIDIC DEVICE FOR THE FUNCTIONAL CO-CULTURE OF HUMAN STEM CELL-DERIVED ISLET AND LIVER ORGANOIDS

Shadab Abadpour*[1;2], Aleksandra Sizenshtadt[1], Chencheng Wang[1;2], Mathias Busek[1;3], Alexey Golovin[3], Justyna Stokowiec[3], Hanne Scholz[2;4], Stefan Krauss[1;3]

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Background: Human energy metabolism is centrally regulated by the pancreatic islets and the liver. There is an urgent need for a reliable human in-vitro model that can recapitulate this feedback-loop. The combination of human pluripotent stem cell (PSC) differentiation, organoids, and organ-on-chip (OoC) technologies offers a novel toolbox for advanced diabetes disease modelling.
Methods: We have developed a pump-less recirculation OoC platform that generates a directional, gravity-driven flow using a 3D-tilting platform for multi-organ culture (UK patent application 2110366.8). Human stem cell-derived liver and islet organoids were cultured for 2 weeks on our chip platform as separate or co-culture with the medium flow on top of organoids. The viability of organoids was evaluated by FDA/PI staining on day 14 of culture. Glucose-stimulated insulin secretion (GSIS) and the levels of albumin and urea were measured on days 1 and 14 of culture.
Results: Islet and liver organoids stayed viable both alone and in co-culture on the platforms over the period of 2 weeks, confirmed by FDA/PI staining. Interestingly, islet organoids on the co-culture system showed improvement in GSIS compared to the mono islet organoids culture ($p<0.05$ vs mono islet on chip). Consumption of insulin and albumin secretion by liver organoids was improved in the co-culture compared to liver organoids cultured alone on chip.
Conclusion: In our proof-of-concept study, we developed a scalable and easy-to-use pump-less OoC platform for the functional co-culture of islet and liver organoids, enabling the crosstalk between them. Both islet and liver organoids showed

improvement in functionality when cultured together. Our platform could have a potential for diabetes disease modelling by combining islet and liver and could be further developed by adding endothelial and immune cells into the chip

OP17

THE QUOD PANCREAS TISSUE BANK AND ATLAS: A UNIQUE RESOURCE FOR TRANSPLANT AND DISEASE-ORIENTED RESEARCH

Nicola Dyson*[1], Sarah Cross[2], Nicole Kattner[1], Minna Honkanen-Scott[1], Morgan Shaw[1], Caitlin Brack[1], Bethany Hunter[1], Yvonne Bury[1;3], Dina Tiniakos[1;4], Dimitrious Bouklas[4], Rowen Coulthard[3], Tracey Davey[5], Sarah Richardson[6], William Scott III[1], Rutger Ploeg[2], James Shaw[1;7]

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Background : The Quality in Organ Donation (QUOD) programme, launched in 2013, is a unique resource to facilitate research into organ donation, transplantation and chronic disease. QUOD provides a repository of samples (tissue, blood, urine) from deceased organ donors in the UK. Researchers are able to combine biological sample analysis with clinical data and patient outcomes, aiding in the search for biomarkers of organ function and improving understanding of injury and repair. Expansion of the project in 2017 enabled the use of whole pancreata with the aim of creating a tissue bank and searchable atlas.

Methods: Pancreata from appropriately consented deceased donors were procured by the UK National Organ Retrieval Service. A standardised tissue sampling methodology was devised for collection of biopsies from 8 defined regions of the pancreas, with tissue preserved for histopathology, EM, transcriptomics and proteomics. Clinical data was collected for incorporation into the atlas. A histological staining panel of H&E, Sirius Red Fast Green and Chromogranin A was performed on tissue sections from all donors and regions. The HALO AI platform was used to quantitatively assess tissue architecture on histological specimens. Transmission EM imaging was undertaken on tissue from head and tail regions.

Results: To date 104 donor pancreata have been collected, including 4 donors with T1DM and 26 donors with T2DM. Histopathology analyses have identified pre-existing tissue pathology, and high throughput quantitative data has been generated on islet, collagen and fat distribution. In addition to evaluation of intracellular organelles, ultrastructural EM studies have revealed alterations in lipid droplet accumulation in T2DM and lipofuscin accumulation in alpha versus beta cells.

Conclusions: The QUOD pancreas collection and atlas provide a valuable resource for investigators into pancreas function, disease and transplantation. Tissue samples suitable for use in a variety of modalities are available, and the selection and request of specimens will be easily accessible via the online atlas portal. Novel insights into tissue geography and ultrastructure obtained through use of samples from the

collection, alongside the standard QUOD sample and data sets, demonstrate the utility and value of the biobank to researchers.

	Summary	Mean	Range
Donor type	60 DBD, 44 DCD		
Age (years)		50.05	6-81
Sex	58 male, 46 female		
BMI (kg/m²)		28.50	17.7-51.4
History of diabetes	4 T1D, 26 T2D		
CIT (hours)		15.21	3.55-50.7

Table 1. Summary of key donor parameters in the QUOD pancreas collection. DBD, Donation after brainstem death. DCD, Donation after circulatory death. BMI, Body mass index. T1D, Type 1 diabetes. T2D, Type 2 diabetes. CIT, Cold ischaemia time.

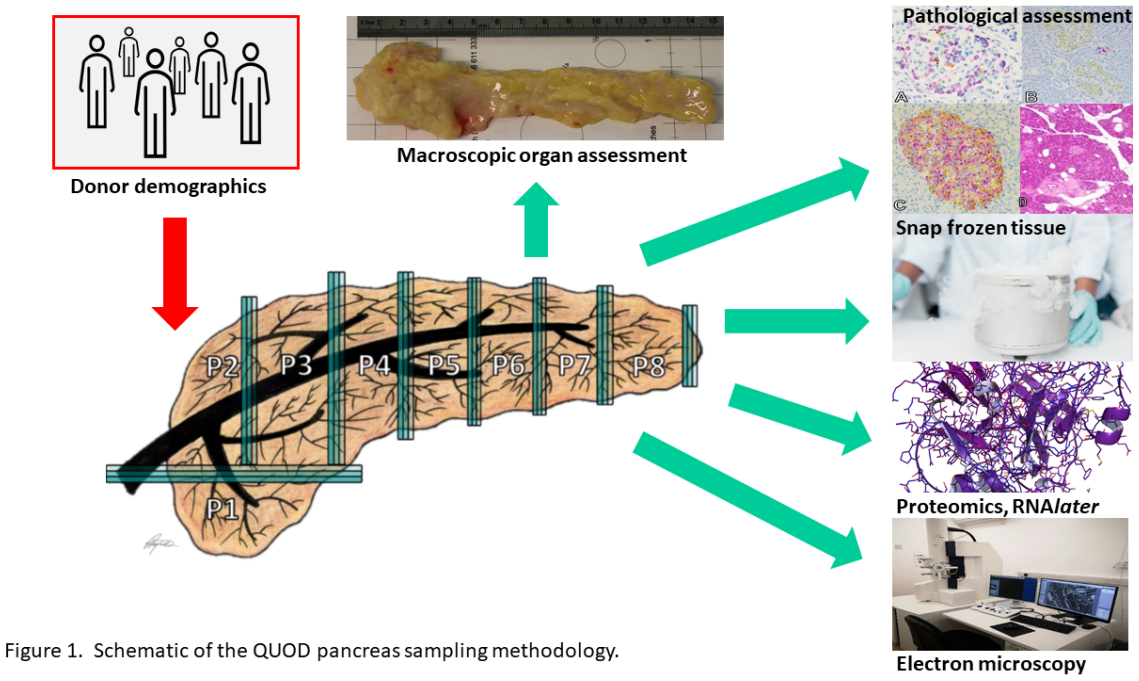

Figure 1. Schematic of the QUOD pancreas sampling methodology.

OP18

ASSESSMENT OF PANCREATIC STEATOSIS AND TRANSPLANT SUITABILITY USING IMAGE-BASED MACHINE LEARNING MODELS

Georgios Kourounis*[1], Pierre Ezuma[2], Mark Turner[2], Sorina Cornateanu[3;4], Lucy Bates[2], Emily Thompson[1;2], Sam Tingle[1;2], Gourab Sen[1], William E Scott[2], Steve White[1;2], Colin Wilson[1;2]

[1]NIHR Blood and Transplant Research Unit in Organ Donation and Transplantation, Institute of Transplantation, Freeman Hospital, Newcastle upon Tyne, United Kingdom, *[2]Newcastle University, Newcastle upon Tyne, United Kingdom*, *[3]The Scottish Liver Transplant Unit, Edinburgh Transplant Centre, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom*, *[4]University of Edinburgh, Clinical Surgery, Edinburgh, United Kingdom*

Background: Assessment of donor organ quality in pancreas transplantation is currently qualitative and reliant on the transplant surgeons' experience and subjective decision-making. Limited inter-rater consensus may limit organ utilisation, especially with 'marginal' organs. This study aimed to develop an image-based machine learning (ML) assessment tool to quantitatively evaluate pancreatic steatosis (PS) and suitability for transplant.
Methods: 214 images from 66 separate donor pancreases were assessed independently by three transplant surgeons for PS and transplant suitability. Six convolutional neural network models pre-trained in image analysis were selected to evaluate these images. They were each trained and tested with 200 and 14 images respectively. 9 organs were fully analysed by microscopic histological assessment, alongside the photographic image analysis.
Results: Accuracy during training for PS and transplant suitability respectively was 48.7-53.8% and 55-75%. Accuracy during testing increased for both variables to 71.4% and 78.6% respectively. Model testing for PS found sensitivity, specificity, and area under receiver operating characteristic (AUROC) to range between 41.7-50.0%, 77.7-84.1%, and 0.33-0.4 respectively. Model testing for transplant suitability found sensitivity, specificity, and AUROC to range between 78.6-83.3%, 0-50% and 0.24-0.7 respectively. Macroscopic visual assessment and microscopic histological analysis for PS was strongly positively correlated, r=0.7650, p=0.0082. Testing 14 images for PS required 0.369 seconds per model.
Conclusions: A quantitative and automated ML model for evaluating donor pancreas organ quality is feasible. Increased accuracy between the training and test phase demonstrates a desired generalisability to novel test images. Larger datasets are required to create a fully functional smartphone camera app to aid decision making and prevent unnecessary pancreas discards.

OP19

ACUTE CELLULAR REJECTION IN PANCREAS BIOPSY SPECIMENS: A TRANSCRIPTOMIC ANALYSIS AND VALIDATION OF THE TISSUE COMMON RESPONSE MODULE (TCRM) SCORE

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Background: Transcriptomic analyses using kidney, heart, liver, and lung transplant specimens has led to the development of the tissue Common Response Module

(tCRM) score based on the expression levels of 11 genes (*BASP1, ISG20*, *PSMB9*, *RUNX3*, *TAP1, NKG7, LCK, INPP5D, CXCL9, CD6, CXCL10)*. This score has not yet been validated in the pancreas. Using a repository of pancreas transplant specimens, we sought to identify patterns of differential gene expression in Acute Cellular Rejection (ACR) and to validate the tCRM score.

Methods: Fifty one formalin fixed paraffin embedded pancreas biopsy specimens: 14 normal, 14 Grade 1 (G1) ACR, 14 Grade 2 (G2) ACR, and 9 Grade 3 (G3) ACR were analysed using multiplex RNA sequencing. Differential gene expression and pathway analyses were performed using a panel of 804 unique genes. Whole transcriptome spatial RNA analysis is ongoing to further compare patterns of gene expression in distinct regions and cell populations.

Results: Significant differences in gene expression were seen in higher grades of rejection. For specimens with G2 and G3 ACR, 18 and 22 genes were differentially expressed respectively. No genes were found to be differentially expressed when comparing G1 ACR to normal biopsy specimens. Pathway analysis demonstrated that the genes enriched in G2 and G3 ACR were most commonly associated with inflammatory pathways like interferon signalling, antigen processing and presentation, and phagocytosis. A statistically significant difference was found in the tCRM scores for G2 ACR and G3 ACR, when compared to the score for normal pancreas tissue.

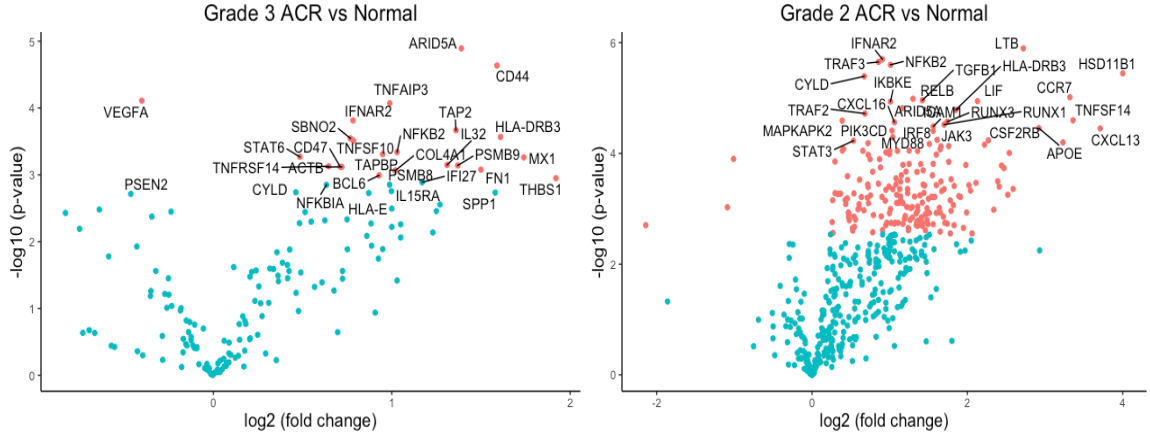
Conclusions: Distinct patterns of gene expression were identified in pancreas specimens with G2 and G3 ACR. The tCRM score for both subsets was significantly elevated when compared with normal pancreas tissue, which is comparable to results seen in kidney, heart, liver, and lung transplant tissue. Further work using spatial transcriptomics and whole transcriptome sequencing will seek to better elucidate the regions and cell populations involved in the development of acute pancreas rejection.

Table 1: tCRM score for normal, G1 ACR, G2 ACR, and G3 ACR pancreas specimens

	tCRM score	95% CI	p-value
Normal	1.78	(1.27, 2.17)	
Grade 1 ACR	1.72	(1.33, 2.19)	0.96*
Grade 2 ACR	2.15	(1.58, 2.41)	0.004*
Grade 3 ACR	2.13	(1.70, 2.48)	0.007*

*p-value for mean tCRM score compared to mean tCRM score for normal specimens

Figure 1: Differential gene expression in G3 ACR and G2 ACR vs. normal pancreas specimens



OP20

COMPARISON OF DIFFERENT HYALURONIC ACID-BASED MATRICES TO IMPROVE HUMAN ISLET SURVIVAL IN MACROENCAPSULATION DEVICES

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Background: Encapsulation of isolated islets has the potential to enable transplantation without the requirement for life-long immunosuppression. However, to date, insufficient oxygen supply is the major challenge for long-term graft survival of macroencapsulated islets. This study investigated the efficiency of different bio-compatible matrices that can deliver oxygen to improve early islet graft survival in macrodevices.

Methods: Isolated human islets (n = 7 DBD donors) were mixed with different matrices: (A) supplemented CMRL, (B) Hyaluronic acid (HA)-based Gel, (C) Beta (β)-Gel (HA-Gel+PFC-emulsion) or (D) preoxygenated β-Gel+O_2. Afterwards, silicone-based macrodevices were loaded with 600 matrix-immersed IEQ (islet equivalents) and cultured for 4 – 5 d. Islet characterisation included yield, counted as islet number (IN) and IEQ; viability (FDA-PI); apoptosis (Annexin V-PI) and reactive oxygen species (ROS) production (DCFH-DA). Parameters were related to IEQ and normalised to preculture data (mean ± SEM).

Results: Results are shown in the table. After culture, a massive islet loss was noted when using CMRL which could be prevented by applicating β-Gel and preoxygenated β-Gel+O_2. Reduction of islet yield correlated with enhanced fragmentation (IN/IEQ ratio) that was highest in CMRL and lowest in β-Gel or β-Gel+O_2. Cell debris accumulation was associated with increased islet ROS production. Again, ROS was highest in CMRL and substantially lower in β-Gel or β-Gel+O_2. In contrast, viability was identical in HA-Gel and β-Gel whilst β-Gel+O_2 provided best preservation of viability. Postculture apoptosis was massively enhanced in CMRL compared with β-Gel and β-Gel+O_2 which showed the lowest increase of apoptosis. Overall survival, defined as survival of viable cells only, was marginal in CMRL and low in HA-Gel. Again, β-Gel+O_2 provided highest protection of overall survival.

TABLE 1 Islet characterisation after 4 – 5 days of 37°C-culture in macroencapsulation devices (n = 7).

Exp. Groups	IEQ Yield (%)	Fragmentation (%)	ROS (%)	Viability (%)	Apoptosis (%)	Overall Survival (%)
(A) CMRL	11 ± 3	421 ± 70	733 ± 403	75 ± 4	1095 ± 228	8 ± 2
(B) HA-Gel	35 ± 8‡	283 ± 80*,†	497 ± 293*	84 ± 2†	716 ± 193*	29 ± 7‡
(C) Beta-Gel	63 ± 5**	158 ± 11**	177 ± 89**	84 ± 3*	345 ± 62***	54 ± 6**
(D) Beta-Gel+O_2	81 ± 7***	152 ± 22***	140 ± 64**	92 ± 5***	337 ± 63***	75 ± 7***

Data are normalized to preculture: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs CMRL; †$P < 0.05$, ‡$P < 0.01$ vs Beta-Gel+O_2

Conclusions: Our study demonstrates that the use of suitable bio-compatible matrices is essential to reduce inflammation and to protect the integrity of macro-encapsulated human islets. As hypoxia is the most decisive factor for islet survival, the efficient delivery of oxygen, even for a limited time, promotes islet survival within macrodevices.

OP21

IDENTIFICATION OF BETA CELL DIFFERENTIATION-PRONE IPSC CLONE FOR CELL THERAPY OF DIABETES

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Background: Induced pluripotent stem cells (iPSCs)-derived β cells are promising candidates for the cell therapy of type 1 diabetes. However, cellular reprogramming generates a variable number of iPSC clones with unpredictable differentiation potential. The aim of this study is the identification of a gene signature for the selection of the best β cell differentiation-prone iPSC clone from a patient.

Methods: Eleven iPSC clones were generated from the same donor. iPSC clones were stabilized and differentiated *in vitro* into cells of the definitive endoderm (DE) stage. The presence of the pluripotency marker OCT4 and the definitive endoderm marker CXCR4 were evaluated by flow cytometry analysis. A gene expression analysis was then performed on the 11 clones at the iPSC and DE stages through Nanostring technology. The expression of 770 genes involved in stemness and trilineage specification was determined and the differential gene expression was correlated with differentiation efficiency. Finally, four iPSC clones were selected and differentiated into mature β cells.

Results: Flow cytometry analysis showed that the 11 iPSC clones, starting with a homogeneous level of pluripotency (Oct4 ≥ 95%), have a heterogeneous differentiation potential at DE stage (45% ≤ Cxcr4 ≥ 96%). Gene expression analysis, at the iPSC stage, revealed 129 differentially expressed genes (P-Adj <0.05), which compartmentalize the 11 iPSC clones into two distinct clusters. The differentiation into β cells of 4 selected iPSC clones belonging to the 2 clusters showed a distinct differentiation efficiency, as mirrored by the insulin-positive cells at the final stage (P <0.01). Furthermore, the analysis of the identified genes, such as ZFHX3, BMP7, KLF4, ROR2, WNT3, involved in the stem cell pluripotency, Hippo, Wnt and TGF-β pathways, directly correlated with the differentiation efficiency.

Conclusions: This study enabled the identification of genes differentially expressed at the pluripotency stage suitable for the selection of the best β cell differentiation-prone iPSC clones from a donor, for future cell therapy. Going forward, the gene signature will be validated on new batches of iPSC from other patients, confirmed at the protein level and gene expression will be tuned at different stages of differentiation.

OP22

NKX6.1: A NEW QUALITY CONTROL TO PREDICT HUMAN BETA CELL FUNCTION POST TRANSPLANTATION.

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Background: For 20 years, our lab has been working on islet transplantation (tx) to restore insulin secretion in type 1 diabetes. Our objective is to guarantee excellent functional human islet grafts. Routine in vivo quality controls represented by the nude mouse bioassays (QIVIPA for Quantitative In Vivo Islet Potency Assay) predicts human islet function in man (r^2=0.16, p<0.0001). However, results are available after clinical tx. In this study, we investigate the use of the Nkx6.1 transcription factor in islet pellets before tx as a predictive marker of beta cell function after islet tx.

Methods: Total RNA of 88 frozen banked clinical human pancreatic islets preparations, was extracted and retro-transcripted in cDNA. Nkx6.1 expression was measured by digital PCR in 58 samples with a RNA Integrity Number RIN > 7. Human islet graft function (mean fasting human c-peptide (hCP)/glycemia) in mice over 1 month was used for correlation studies. The Primary Graft Function (PGF) of human recipients and islet function in mice, were analyzed with a ROC curve to determine a minimum threshold of Nkx6.1 copy number (cp), resulting in optimal PGF in corresponding recipients (betascore > 7). Islets were pretreated with silymarin and resveratrol to boost Nkx6.1 expression and potentially improve function.

Results: In 58 human islet grafts, graft function in mice was correlated with the total cp of Nkx6.1 mRNA in islets before tx (r^2=0.19; p=0.0006). We previously showed ≥5268 ng/g hCP/glycemia is required in our surrogate in vivo quality control to achieve optimal PGF in tx recipients (or 5268/3 grafts =1746 ng/g per graft). By using the minimum threshold of islet function per graft, we determined the minimum threshold of Nkx6.1 copy number per clinical islet preparations with a ROC curve to be 1,59 M per preparation (or 1%). In vitro treatment of islets boosted Nkx6.1 and enhanced in vivo function.

Conclusions: These results show that the quantification of Nkx6.1 mRNA cp on human islets before tx, can be a good predictive factor in the selection of the most functional grafts prior to tx in man. However, the direct link of Nkx6.1 in islet function has to be analyzed by specific targeting of Nkx6.1. Prospective studies are in progress to confirm the minimum threshold and to include this test in our quality controls prior to release for clinical tx.

OP23

ENDOTHELIAL GLYCOCALYX SHEDDING IN PATIENTS UNDERGOING PANCREAS TRANSPLANTATION

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Background: The vascular endothelium is critically involved in many steps of tissue damage originating during ischemia-reperfusion (IR) in human transplantation. An endothelial surface layer, the glycocalyx, forms the primary interface between the blood and the healthy endothelium and its shedding is recognized as a cornerstone in IR-related endothelial dysfunction. We investigated the role of endothelial glycocalyx breakdown products in patients undergoing pancreas transplantation.
Methods: Endothelial integrity and remodelling products were measured in plasma from 26 simultaneous reno-pancreas transplants and 2 re-transplants recipients. The levels of syndecan-1, hyaluronan, heparan sulfate and Vascular Endothelial Growth Factor (VEGF) were determined using enzyme-linked immunosorbent assay at different time points: before surgery, 10 minutes and 24 hours after reperfusion, and at patient discharge.
Results: Transplant recipients had greater evidence of glycocalyx damage 10 min. after reperfusion of the graft as compared before surgery, measured by plasma levels of syndecan-1 (66.54 vs 155ng/mL; $p<0.0001$) and heparan sulfate (4.96 vs 6.07 ng/mL, $p=0.0435$) components. However, plasma hyaluronan levels remained unchanged throughout. The levels of VEGF significantly decreased in plasma 10 min. after graft reperfusion (117 vs 18 pg/mL; $p<0.0001$). No correlation existed between endothelial markers except for syndecan-1 with VEGF and heparan sulfate at this time point, respectively ($r=0.395$, $p=0.0371$; $r=0.572$, $p=0.001$). Regression analysis showed that the higher levels of syndecan-1 were more frequent in patients with acute rejection ($p=0.011$), intestinal complications ($p=0.045$) and those who developed kidney surgical complications ($p=0.026$) or needed for a urological reintervention ($p=0.024$). Graft pancreatitis and pancreatic fistulas were associated with the levels of hyaluronan at 24h post-reperfusion ($p=0.04$; $p=0.04$, respectively) and at patient discharge ($p=0.012$; $p=0.012$, respectively).
Conclusions: This study provides the first evidence for endothelial glycocalyx damage in pancreas transplantation. Further studies are needed to validate these findings in a larger sample size.

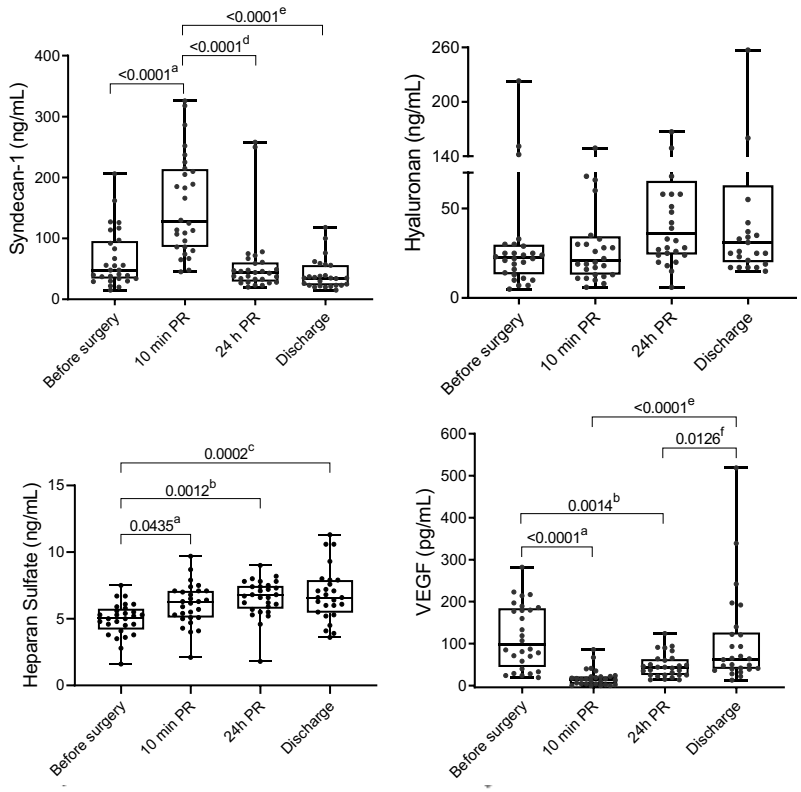

Figure 1. Plasma levels of endothelial glycocalyx and remodelling breakdown products over time during human pancreas transplantation. Boxes represent the interquartile ranges and whiskers extend to the minimum and maximum values. The median values are shown within the boxes. Each dot represents one individual patient. P-values of less than 0.05 were considered statistically significant. No p-value is shown in the figure when ≥0,05. [a] t=0 vs t=10 min PR, [b] t=0 vs t=24h PR, [c] t=0 vs t=Discharge, [d] t=10 vs t=24h PR, [e] t=10 min PR vs t=Discharge, f t=24h PR vs t=Discharge. No p-value is showed when ≥0,05. PR, Post-Reperfusion. VEGF, Vascular Endothelial Growth Factor.

	Syndecan-1							
Clinical characteristics	Before surgery		10min PR		24h PR		Discharge	
	r	*p*	r	*p*	r	*p*	r	*p*
Donor age	0.189	0.334	-0,379	0.046*	0.268	0.167	-0.163	0.424
Lipase (Discharge)	0.124	0.529	0.404	0.032*	0.070	0.721	0.366	0.065
Creatinine (pre-transplant)	0.434	0.02*	0.275	0.155	0.443	0.018*	0.202	0.321
Creatinine (24h PR)	0.341	0.075	0.267	0.169	0.467	0.012*	0.288	0.152
	Heparan sulfate							
Clinical characteristics	Before surgery		10min PR		24h PR		Discharge	
	r	*p*	r	*p*	r	*p*	r	*p*
Donor age	0.016	0.933	-0.4	0.034*	-0.315	0,101	0.044	0.829
Recipient age	0.335	0.080	0.48	0.009*	-0.030	0.875	-0.111	0.586
DM vintage	0.154	0.431	0.491	0.007*	0.103	0.600	-0.219	0.281
Creatinine (pre-transplant)	-0.244	0.21	-0.185	0.344	-0.501	0.006*	-0.378	0.056
Creatinine (24h PR)	-0.221	0.258	-0.173	0.376	-0.39	0.039*	-0.315	0.116
Creatinine (Discharge)	-0.17	0.387	0.026	0.894	-0.527	0.003*	-0.246	0.224
	Hyaluronan							
Clinical characteristics	Before surgery		10min PR		24h PR		Discharge	
	r	*p*	r	*p*	r	*p*	r	*p*
Donor BMI	-0.552	0.003*	-0.390	0.048*	-0.216	0.265	-0.429	0.041*
Dyalisis vintage	0.082	0.676	0.044*	0.821	0.397	0.036	-0.036	0.861
ICU days	0.182	0.383	0.544	0.004*	0.217	0.296	0.174	0.425
	VEGF							
Clinical characteristics	Before surgery		10min PR		24h PR		Discharge	
	r	*p*	r	*p*	r	*p*	r	*p*
Donor BMI	0.361	0.069	0.194	0.341	0.366	0.065	0.470	0.020*
Recipient age	0.292	0.130	0.362	0.057	0.392	0.038*	0.261	0.196

TABLE 1. Correlation between endothelial damage components levels and various clinical parameters. *p< 0.05. PR, post-reperfusion; DM, Diabetes Mellitus; BMI, Body Mass Index; ICU, Intensive Care Unit; VEGF, Vascular endothelial growth factor. r, Spearman's correlation coefficient; *p*, P value.

OP24

PANCREATIC ISLET NUMBER AND DECEASED ORGAN DONOR FACTORS AS ATOOL FOR PANCREATIC DONOR ASSESSMENT FOR TRANSPLANTATION

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Background: Pancreas transplantation is a near cure treatment for type 1 diabetic patients. Nowadays, 5-year patient survival is over 90% and only 6% of graft are lost after 90 days. Nonetheless, annual activity of pancreatic transplantation in Spain declines each year, while keeping enormous donation rates. Half of donated pancreata are ruled out based on both age and gross exam and 40% of the viable ones for transplantation are declined. We correlate deceased donor clinical and laboratory parameters with the number of islets in the graft and their utility as a predictive tool for pancreatic graft assessment.

Methods: We analyze every discarded donation done in our center from March 2018 to October 2022 due to age or clinical conditions. Clinical variables were recorded, and Number of Islets (NOI) was counted in pancreatic head histological slices. NOI is the mean of islets reported by two pathologists in 1 cm2 areas. A descriptive analysis of all the clinical and laboratory variables collected was made. Statistical correlation between NOI per cm2 and variables was made by Student's t test, ANOVA and linear regression. Secondly, 2 age groups were established (<40 years old (n=20) and >70 years old (n=37)) and we compared the NOI per cm2 between the two by using Propensity Score Matching (PMS) for a sample of 11 pairs of patients with identical levels of serum amylase, sodium and creatinine in ICU and type of donor.

Results: We analyzed 162 pancreata (Table 1). The mean age of donors was 58.6 years, 78% of them were DBD (n=127) and 24% DCD (n=35). Stroke was the cause of death in 62% of the cases (n=101). Biopsies yielded a mean NOI of 32.5 ± 17.8 per cm2. As for the association between donor characteristics and NOI, no differences were found in subgroup analysis (Table 2). After statistical analysis, only donor serum amylase levels (lower amylase levels with higher NOI) and donors who died of CNS tumors (mean NOI 55 ± 11) correlated with NOI. No significant differences were found in the NOI between the two age groups.

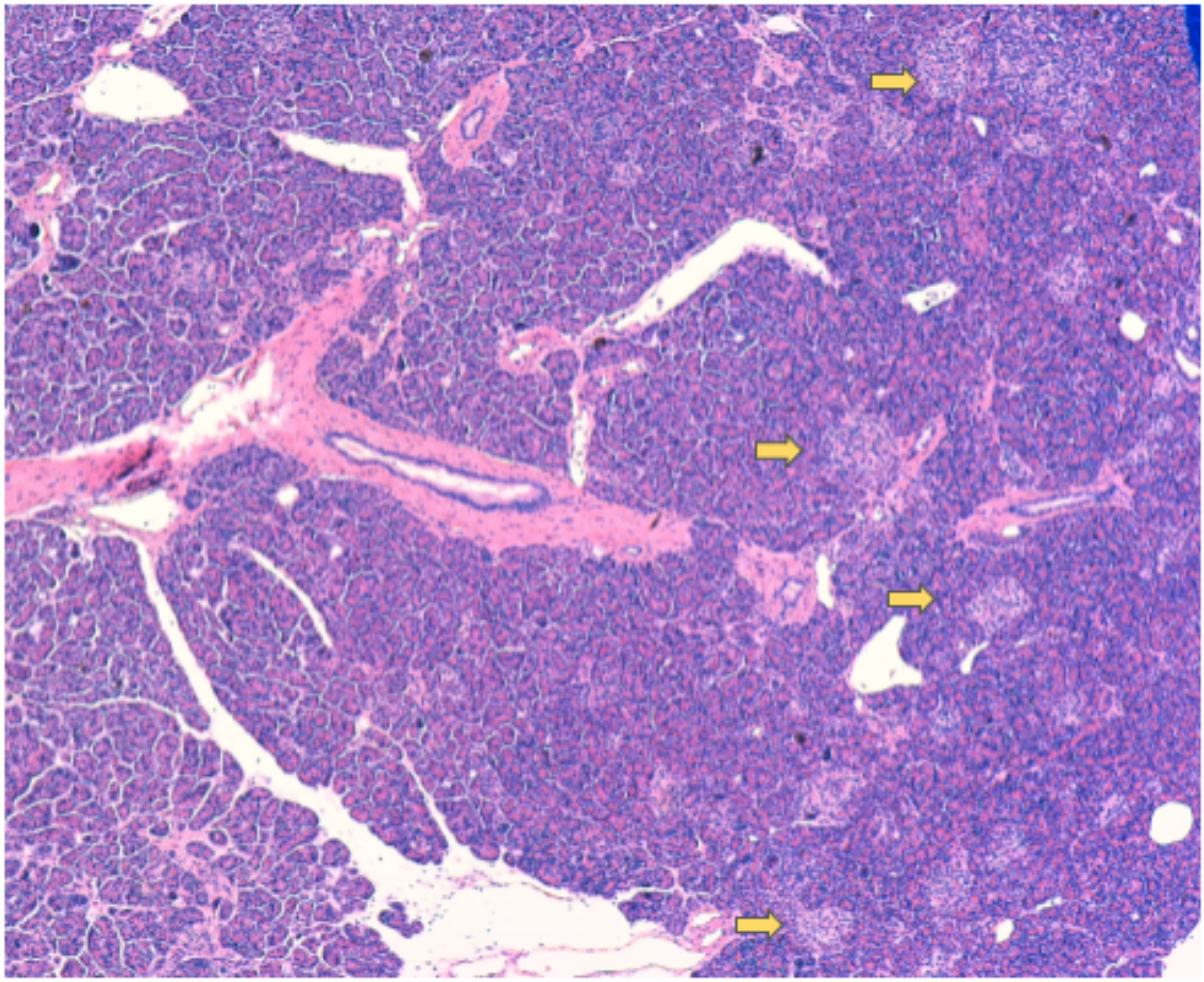
Conclusions: Serum amylase may be used for assessment of pancreas donors. Donors deceased of CNS tumors could be nearly optimal donors. Age per se does not seem to be related to a significant decrease in the number of Langerhans islets and neither the cause of death.

Donor, n (%)	n=162
DBD	127 (78)
DCD-NRP	29 (18)
DCD-SRR	3 (2)
DCD-TANRP	3 (2)
Cause of death, n (%)	
Stroke	101 (62)
TBI	26 (16)
HBI	25 (15)
CNS Tumors	6 (4)
Others	4 (3)
Age (y)	58.6 (8-86)
Sex (male/female) (%)	63/37
BMI (kg/m^2)	26 (16.7-39)
Stay in the ICU (h)[a]	4.5 ± 5.1
Use of vasoactive drugs, n (%)	101 (62)
Hypertension, n (%)	71 (44)
Smoking, n (%)	44 (27)
Arteriosclerosis, n (%)	15 (9)
Alcohol, n (%)	28 (17)
Blood test parameters[a]	
Plasmatic sodium (mmol/L)	145 ± 7.2
Serum amylase (U/L)	59 ± 129.5
Serum creatinine (mg/dL)	0.9 ± 0.9
Glucose (mg/dL)	169 ± 170.8
Pancreatic Islets/cm^2 [a]	32 ± 18

Table 1.

	Pancreatic Islets/cm^2	**p**
Sex[a]		
Male	31 ± 13	> 0.05
Female	35 ± 23	
Use of vasoactive drugs[a]		
Yes	32 ± 19	> 0.05
No	33 ± 16	
Hypertension[a]		
Yes	30 ± 14	> 0.05
No	34 ± 20	
Smoking[a]		
Yes	30 ± 12	> 0.05
No	34 ± 19	
Arteriosclerosis[a]		
Yes	28 ± 8	> 0.05
No	33 ± 18	
Alcohol[a]		
Yes	30 ± 10	> 0.05
No	33 ± 19	

Table 2. [a]Mean ± SE



Haematoxylin-eosin. 10X. Section of pancreatic parenchyma in which the lobular structure of the normal pancreas can be identified. On the right side of the image, marked with yellow arrows, rounded structures can be seen, composed of cells of a paler appearance that correspond to the islets of Langerhans (endocrine pancreas). The remaining cells, more basophilic and reddish in appearance at low magnification, correspond to the acini of the exocrine pancreas.

OP25

BIOFABRICATION OF A FUNCTIONAL XENOGENIC VASCULARIZED ENDOCRINE PANCREAS (VEP) FOR TYPE 1 DIABETES

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Background: Intrahepatic islet transplantation in patients with T1D is limited by donor availability and lack of engraftment. To overcome these limitations, based on our

experience with decellularized rat lung as scaffold repopulated by murine islets and HUVEC cells for the generation of Vascularized Islet Organ, we prototyped our platform to engineer an upgrade based on human blood outhgrow endothelial cells (BOECs) and immature neonatal porcine islet clusters (NPIs).
Methods: Rat lung was decellularized and seeded with NPIs and BOECs, generating a Vascularized Endocrine Pancreas (VEP). For *ex vivo* maturation VEP was cultured for 7 days in a bioreactor designed to allow cell integration. The β cell death in mature VEPs was estimated during *ex vivo* organ maturation by miR-375 expression. VEPs and control NPIs function were measured by dynamic insulin secretion test and polyhormonal quantification (ELISA/IF).Subsequently, VEPs were subcutaneously transplanted in diabetic NSG mice and compared with NPIs transplanted in different sites: kidney capsule (KC-NPIs), deviceless (DL-NPIs) and liver (LV-NPIs).
Results: VEPs showed a regenerated vascular network ($CD31^+$) with NPIs (INS^+) integrated. miR-375 was expressed in NPIs but not in BOECs, as expected. VEP was able to significantly reduce β cell death: the amount of lost NPIs were ≤ 5% during VEPs maturation compared to >71% of the standard culture ($p<0.05$). VEPs were able to sustain NPIs engraftment, survival and significantly improve insulin secretion during the maturation process compared to control NPIs (AUC: VEPs Vs NIPs $p<0.01$). VEPs, transplanted in diabetic NSG, demonstrated a significant superior NPIs engraftment with a prompt function after implantation (3 days) and the preservation of the normoglycemic status until 18 weeks compared to all the internal controls (KC-NPIs, DL-and LV-NPIs).
Conclusions: *V*EP technology is able to foster the NPIs functional endocrine maturation in vitro, but it is also able to perform in vivo immediately upon transplantation and for over 18 weeks, compared to normal performance within 8 weeks after implantation in various state of the art preclinical models. Given the recent progress in genetic engineering of NPI donor pigs, this technology may enable the assembly of immune-protected functional endocrine organs.

OP26

OVEREXPRESSION OF HPD-L1 IN NEONATAL PORCINE ISLETS IMPROVES LONG-TERM XENOGRAFT SURVIVAL IN HUMANIZED NSG MICE

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Background: Strong xenorejection limits the clinical application of porcine islet transplantation in type 1 diabetes. Targeting T cell-mediated response is one of the main approaches to improve long-term graft survival. Here we studied the effects of genetic modified porcine islet grafts with expression of human programmed death-ligand 1 (hPD-L1) to suppress rejection in diabetic humanized NOD-scid IL2Rgnull (NSG) mice.
Methods: We isolated pancreatic islet-like clusters from transgenic neonatal pigs overexpressing hPD-L1 and from wild type animals. We transplanted clusters into streptozotocin-induced diabetic NSG mice carrying an established human immune system (16-20 weeks after transfer of cord blood-derived hCD34+ cells; hPD-L1 group,

n=10; wild type group, n=6). Our primary endpoint was normoglycemia (random non-fasting blood glucose levels < 180 mg/dl) at day 120 after transplantation.
Results: Compared to wild type group, the hPD-L1 group achieved superior normoglycemia rate (50% versus 0%, p<0.05) and significant higher plasma C-peptide levels indicating long-term beta cell function. In histological analysis, animal transplanted with hPD-L1 expressing grafts exhibited less infiltration with hCD45+ cells and larger insulin positive graft areas. In situ hybridization staining showed that infiltrating cells in hPD-L1 group expressed significant less human IFN-γ as compared to the wild type group.
Conclusions: We here demonstrate for the first time that overexpression of hPD-L1 in porcine islets exerts a strong protective immunomodulatory effect in a humanized mouse model. These findings support the hypothesis that hPD-L1 has the capacity to control cellular rejection and therefore represents one promising candidate transgene for clinical porcine islet xenotransplantation.

OP27

ISLET ISOLATION AND TRANSPLANTATION OUTCOMES FROM DONATION AFTER CIRCULATORY ARREST DONORS IN THE UK

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Background: Islet cell transplantation was commissioned by the National Health Service in the UK in April 2008. Data on transplant outcomes was collected centrally on the UK Transplant Registry from 2010 and retrospectively collected from 2008. Solid organ donation after circulatory arrest (DCD) donors have been increasing over the last 10 years.
Methods: Islet isolations and transplant activity in the UK by donor type in the period 1 April 2008 to 31 March 2021 were analysed. For first routine islet transplants one year graft survival, using the Kaplan-Meier method, and metabolic outcomes were compared between the two donor types.
Results: During the time period, there were 1245 deceased donors whose pancreas was accepted and retrieved for islet isolation: 1052 donation after brain death (DBD) and 193 DCD. Isolation commenced in 920 (96%) of 957 DBD and 158 (97%) of 163 DCD donors where information was available. Of those where isolation commenced, isolation was completed in 79.4% of DBD and 78.5% of DCD donors. Of the donors with isolation completed, the proportion transplanted was 31% of 730 DBD and 25%

of 124 DCD donors, though not statistically significantly different, Chi-Square test p=0.2.
There were 314 islet transplants, 275 (88%) DBD and 39 (12%) DCD donors. There were 158 DBD and 23 DCD first routine islet transplants and graft follow-up was available for 155 DBD and 23 DCD transplants. There was no statistically significant difference in one year graft survival between the donor types, 87% for DBD and 82% for DCD, log-rank p-value=0.62. In both the DBD and DCD groups at one year post transplant, the median HbA1c was 51 mmol/mol and the median number of severe hypoglycaemic events was 0. The proportion of patients achieving insulin independence in the first year, where known, was 23% and 25% for DBD and DCD, respectively. Of the 23 patients receiving a DCD graft, 17 (74%) have received a second priority graft compared with 94 (59%) of 158 patients receiving a DBD graft, although not statistically significantly different, Chi-Square test p=0.18.
Conclusions: There was no significant difference in the proportion of isolations being transplanted between DBD and DCD donors. Although the number of first islet grafts from DCD donors was small, no significant difference in one year graft outcome was found compared with DBD donors.

OP28

ISLET TRANSPLANTATION VERSUS INSULIN ALONE IN TYPE 1 DIABETIC KIDNEY TRANSPLANT RECIPIENTS: A FRENCH NATIONWIDE STUDY ON BEHALF OF THE TREPID GROUP.

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Background: Islet transplantation is associated with a benefit on glycaemic control compared to optimized insulin therapy in recent clinical trials. However, there is a lack of evidence concerning the long-term impact of islet transplantation on type 1 diabetic kidney transplant recipients' prognosis.
Methods: Every type 1 diabetic recipient transplanted with a kidney in France between 2000 and 2017 was included. Patients transplanted with pancreatic islets were compared to controls treated with insulin alone according to a matching method based on time-dependent propensity scores (using the following variables : yera of transplantation, donor age, and recipient age, serum creatinine, HBA1c, BMI, cardiovascular background) which allow to ensure patients comparability at the time of islet transplantation. The primary outcome was graft failure, defined by death or return to dialysis.
Results: Among 2393 type 1 diabetic patients transplanted with a kidney during the study period, 381 were eligible to islet transplantation, including 47 that were actually transplanted with islets. Median time for islet transplantation was 34.8 months [21.8-48.4]. Probabilities of insulino-independence and islet graft survival at 1, 5 and 10 years were respectively 63.8% [51.5-79.2], 46.3% [33.9-63.2], 38.7% [25.9-57.8] and 89.4% [81.0-98.6], 87.2% [78.2-97.3], 78.2% [66.2-92.4]. After matching, we observed a

significant benefit of islet transplantation compared to insulin alone on graft failure, with a HR of 0.48 [0.20-0.94], mainly explained by a protective effect on the risk of death (HR= 0.38 [0.11-0.95]). We finally estimated the life-expectancy for a 10-year follow-up and found 9.61 years [9.02-10.00] in the islet transplantation group versus 8.85 years [7.97-9.56], with a difference of 8.88 months [-2.16-20.44]
Conclusions: We observe a significant benefit of islet transplantation on the risk of graft failure and death in type 1 diabetic kidney transplant recipients. These results provide incentives to promote islet transplantation in this population.

OP29

PRIMARY GRAFT FUNCTION PREDICTED 5-YEAR OUTCOMES OF ISLET ALLOTRANSPLANTATION: A RETROSPECTIVE COHORT STUDY FROM THE CITR IN 1210 T1D PATIENTS

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Background: Allogeneic islet transplantation (IT) is a validated therapy in type 1 diabetes. The mechanisms underlying the decline of islet graft function with time are unclear. We evaluated the distinct relation between primary graft function (PGF) and 5-year IT outcomes.
Methods: This retrospective multi center cohort study enrolled all participants from the Collaborative Islet Transplant Registry, who received IT alone, or after kidney transplantation, between 01/19/1999, and 07/17/2022. Exposure was PGF, measured 28 days after last islet infusion with a validated composite index of islet graft function (Beta2-score). Primary outcome was 5-year incidence of unsuccessful IT, and secondary outcomes were graft exhaustion, inadequate glucose control and the need for exogenous insulin. Relation between PGF and IT outcomes was explored with a competing risk analysis adjusted for all covariates suspected or known to impact outcomes. A predictive model based on PGF was built and internally validated by using bootstraps resampling method.
Results: In 39 centers, 1210 patients (712 (59.5%) females, mean (SD) age 47 (11) years) received in total a median (IQR) of 11,800 (8,700-15,900) 150µm islet-equivalents per kg of recipient weight. PGF was 14.3 (8.8). The 5-year cumulative incidence of unsuccessful IT was 70.7% (95%CI 67.3-73.8), and inversely and linearly related to PGF with adjusted subhazard ratio (sHR) of 0.77 (95% CI 0.72-0.82) per 5 units of Beta2-score (p<0.0001). Secondary endpoints were similarly related to PGF. PGF predicted 5-year cumulative incidences of unsuccessful IT, graft exhaustion, inadequate glucose control, and the need for exogenous insulin with a good accuracy as shown by the median (range) C-statistic values of 0.70 (0.69-0.71); 0.76 (0.74-0.77); 0.65 (0.64-0.66); 0.72 (0.71-0.73), respectively.
Conclusions: This global multicenter study demonstrated an independent and linear relation between PGF, measured one month after last islet infusion, and 5-year clinical outcomes of IT, independently of the number of infusions, total islet mass transplanted,

and immunosuppression regimen. Our results also suggested that a simple model based on PGF can predict long term IT outcomes with reasonable accuracy.

OP30

METABOLIC OUTCOMES AFTER PANCREAS TRANSPLANT ALONE FROM DONATION AFTER CIRCULATORY DEATH DONORS-THE UK TRANSPLANT REGISTRY ANALYSIS

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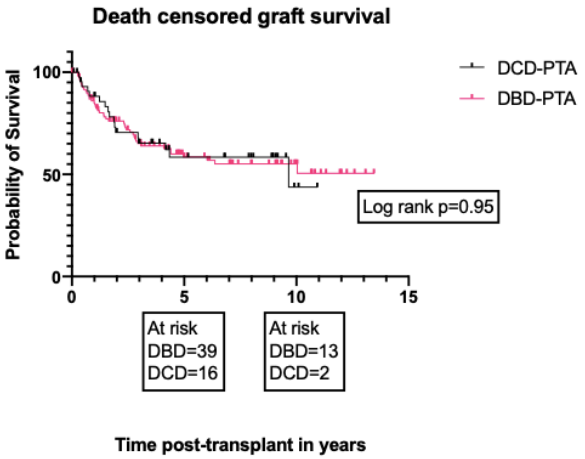
Background: Extrapolating data from early DCD (donation after circulatory death) kidney transplantation, pancreas transplants from DCD grafts were feared to have worse metabolic outcomes. Hence, we aimed to address the question of solitary pancreas transplant from DCD donors- are our concerns justified?
Methods: A UK registry analysis of 185 PTA (pancreas transplant alone) performed from 2005 to 2018 was conducted. All early graft losses (<3 months) were excluded in this analysis to allow focus on the metabolic outcomes. The primary aim was to compare the metabolic outcomes between DBD (donation after brainstem death) & DCD grafts (HbA_1C, weight gain & incidence of secondary diabetic complications); secondary aim was to compare rejection rates (including the need for steroids), patient & graft survival between the two groups. Functioning graft is defined as remaining insulin independent. Secondary diabetic complications are defined as any of the following events: myocardial infarction, cerebrovascular accident, limb amputations
Results: After excluding early graft losses (n=23, DBD=16 & DCD=7); data from 162 PTA (DBD=114 & DCD=48) were analyzed to compare the metabolic outcomes. The average functional warm ischemia time (time from systolic BP<50mmHg to commencement of perfusion) for DCD group was 17$\pm$5.1 mins. Transplant characteristics & outcomes as shown in table-1. BMI of the donor was less in DCD cohort (DBD=23.40 vs. DCD=22.25, P=0.006). Both the DBD & DCD recipients had similar rates of depleting antibody induction & de novo steroid usage (Table-1). The steroid-free maintenance rates were equivalent in both the groups (DBD=75% vs. DCD=73%, p=0.79). There were no significant differences in the HbA_1C, weight gain, rejection rate, & incidence of secondary diabetic complications post-transplant between DBD & DCD recipients (Table-1). The 1-, 5-, &10-years patient and graft survival were similar in both the groups (Figure-1).
Conclusions: This is the first & the biggest study worldwide reporting equivalent metabolic outcomes and survival (patient/graft) after PTA from DCD grafts to that of DBD grafts with more than 10-years follow up.
Figure-1



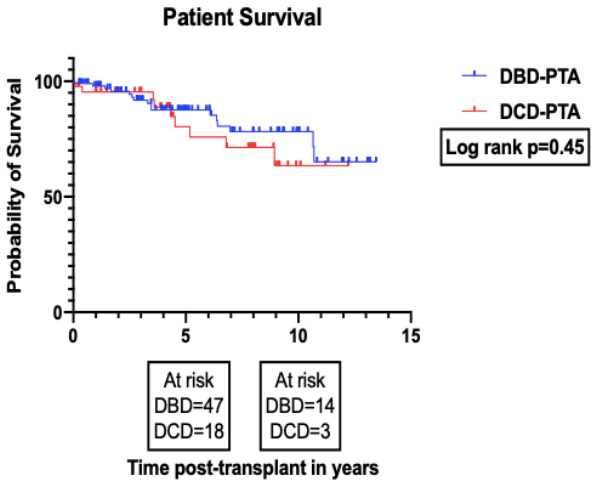


Table-1

Transplant characteristics and Outcomes	DBD	DCD	P value
Donor age in years-Median	33	29	0.11
Donor BMI in kg/sq.m- Median	23.40	22.25	0.006
Donor abdomen girth in cm-Median	84	81.5	0.14
Recipient age in years- Median	41	43	0.63
Recipient BMI in kg/sq.m- Median	24.65	24.40	0.62
Recipient HbA_1C at registration in mmol/mol-Median	76	75	0.52
Recipient insulin use at registration in IU/Day-Median	40	40	0.80
% of sensitized recipient (CRF>5%)	36	29	0.39
% of highly sensitized recipient (CRF>85%)	8.7	10.4	0.73
Cold ischemia time (mins)-Median	688	720	0.19
0 DR mismatch (%)	24.5	14.5	0.15
1 DR mismatch (%)	51	48	0.72
2 DR mismatches (%)	24.5	37.5	0.09
Bladder drainage (%)	33.3	35.4	0.79
Depleting antibody induction (%)	81	87.5	0.31
Non-depleting antibody induction(%)	19	12.5	0.31
De-novo steroid usage (%)	18	17	0.87
IFCC HbA_1C at 3-months-Median, in mmol/mol (Functioning grafts)	36	32	0.08
IFCC HbA_1C at 1-year-Median, in mmol/mol (Functioning grafts)	34	36	0.25
IFCC HbA_1C at 3-years-Median, in mmol/mol (Functioning grafts)	35	33	0.39
IFCC HbA_1C at 5-years-Median, in mmol/mol (Functioning grafts)	36	35	0.49
% Weight gain at 3-months (Functioning grafts)	-4.5	-1.4	0.20
% Weight gain at 1-year (Functioning grafts)	-1.8	-1.6	0.60
% Weight gain at 3-years (Functioning grafts)	0.2	-1.1	0.41
% Weight gain at 5-years (Functioning grafts)	1.5	1.5	0.95
Rejection rate at 3-months (%)	10	12.5	0.63
Rejection rate at 1-year (%)	19	10	0.15
Rejection rate at 3-years (%)	12	10	0.71
Rejection rate at 5-years (%)	10	10	1.00
Secondary diabetic complications at 3-months(%)	0.8	2	0.51
Secondary diabetic complications at 1-year(%)	-	-	-
Secondary diabetic complications at 3-years(%)	-	-	-
Secondary diabetic complications at 5-years(%)	-	-	-

CLINICAL CASES

CC01

SEVERE ACUTE REJECTION IN PANCREAS AFTER KIDNEY TRANSPLANTATION: A CASE PRESENTATION

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Background: Acute rejection following pancreas after kidney (PAK) can result in graft loss, with associated morbidity and mortality. There is little evidence for optimum management. We present a case of severe acute rejection in a PAK recipient.

Case presentation: A 32-year-old female underwent a PAK transplant (DBD, HLA 2:1:0), after a live donor kidney transplant 5 years earlier. Duodenoduodenal anastomosis was used at implantation. Induction was with Alemtuzumab, followed by standard maintenance regimen (tacrolimus, mycophenolate mofetil and prednisolone). The recipient was readmitted with a rise in serum amylase and lipase 5 months post-transplant. Amylase and lipase peaked at 1528u/L and >3000u/L, respectively. CT demonstrated pancreas graft oedema, suggestive of graft pancreatitis (figure 1). Endoscopic biopsy of donor duodenum showed severe ulceration, with no cause identified. The recipient had low IgG4 subclass immunoglobulins and newly positive for anti-GAD antibody. The recipient was treated for presumed rejection with pulsed methylprednisolone and antithymocyte globulin (ATG), titrated to CD3 count. CT-guided pancreas graft biopsy showed acute T-cell mediated rejection, with septal fibrosis, minimal C4d staining and negative donor specific antibodies. Sirolimus was introduced into maintenance immunosuppression following biopsy. Normal renal function was maintained throughout the rejection episode, with good glycaemic control. Following addition of sirolimus, amylase and lipase remained high with a C-peptide level of 0.54nmol/L. Consideration was given to further ATG and steroids, however on discussion with the recipient, the risks of malignancy and/or severe infectious complications associated with further ATG were not justified given that the recipient had optimal beta-cell function (Igls criteria) and a beta-2 score 31.02. The recipient was restarted on insulin 449 days post-PAK transplant.

Conclusions: We present a complex case of acute severe rejection in a PAK recipient, resolving following addition of sirolimus. Although duodenoduodenostomy provided endoscopic access for biopsy, CT-guided biopsy confirmed the diagnosis. Graft biopsy and treatment of severe acute rejection represent significant challenges, with evidence limited to single centre case series.

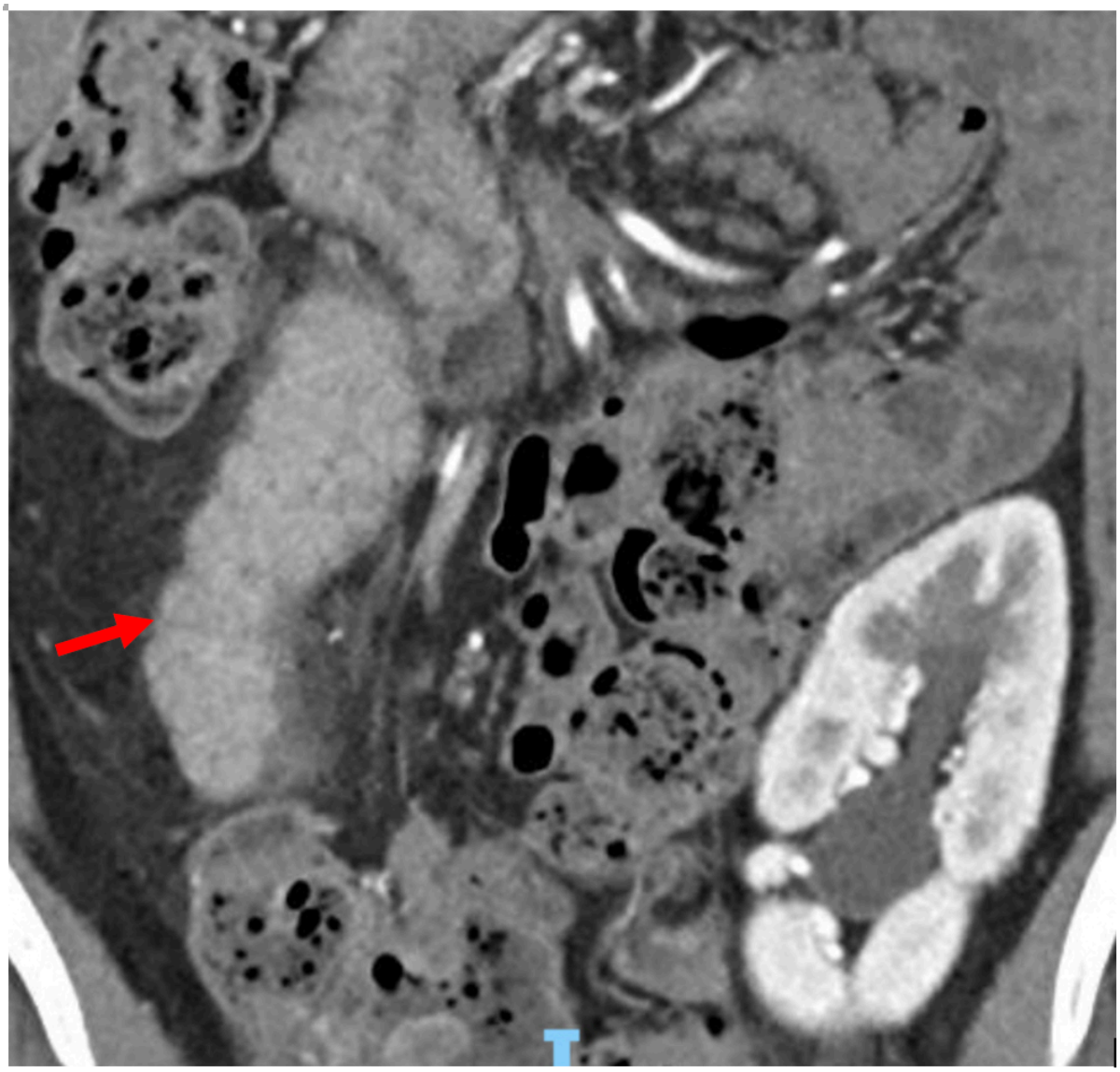

Figure 1 – CT demonstrating parenchymal oedema and surrounding inflammatory stranding, suggestive of graft pancreatitis.

CC02

SIMULTANEOUS PANCREAS-DUAL KIDNEY TRANSPLANTATION: A CASE REPORT

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Background. Quality of pancreas and kidney grafts from deceased donors can be extremely wide and age is not a reliable parameter of evaluation. In case of dubious clinical data, biopsy used to evaluate the graft and decide whether to perform a single or a double kidney transplant. We present a case involving a young donor with a kidney biopsy score unexpected in relation to her age and known comorbidities

Methods. Organs from a 43year-old woman (BMI 31.0 Kg/m^2), brain dead donor due to cerebral hemorrhage, CMV IgG positive, KDPI 46%, KDRI 0.96, PDRI 1.88, were offered for an SPK transplant. Donor apparently had no comorbidities but a serum creatinine of 1.5 mg/dl (e-GFR 40.9 ml/min, worsened during the observation period. Wedge kidney biopsies (159/208 glomeruli) were performed, graded according Karpinski-Remuzzi score 8/12 for each of the two kidneys (glomerular sclerosis: 1/3, tubular atrophy: 2/3, interstitial fibrosis: 2/3, arterial narrowing: 3/3). Due to these unexpected data, it was performed a SPDoubleK transplantation on a 49year-old man with type 1 diabetes, laser treated diabetic retinopathy and end stage renal disease on dialysis (since 4 years).
Results. Transplantation was performed placing pancreas in retrocolic position, systemic-enteric drained and completed placing the left kidney in the left iliac fossa and the right kidney in right iliac fossa. Cold ischemia time lasted 485 min for pancreas, 600 min for right kidney and 680 min for left kidney. Induction was obtained with basiliximab and steroids. Maintenance was based on LCP tacrolimus, mycophenolic acid (720 mg twice a day) and steroids, rapidly tapered. On POD 7, recipient suffered of spontaneous pneumothorax. The following postoperative period was uneventful and he was discharged with 1.7 mg/dl serum creatinine. At 1-year follow-up he is insulin-independent and serum creatinine is 1.8 mg/dl.
Conclusions. According to Karpinski-Remuzzi's criteria, the high biopsy score would not have allowed the single kidney transplant. It was also conflicting with the donor's age that would not have required a biopsy based on her medical history. However, it was decided to perform a SPDKTx to improve the patient outcome. The donor kidney biopsy remains a very helpful tool in the evaluation of the graft. However, it is a data to be interpreted case-by-case.

CC03

PANCREAS TRANSPLANTATION IN HIGHLY SENSITIZED PATIENT

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Background: Highly sensitized (HS) patients accumulate on waitlists worldwide due to matching difficulty and inequity of allocation policies. There has been a scarcity of studies regarding pancreas transplantation(PT) in HS patients.

Case Report: A 48-year-old man, type 1 diabetes since the age of 18 underwent a living-donor kidney transplant in August 2009. Pre-transplant c-PRA was zero and kidney mismatch was 122. There was a vascular rejection successfully treated with Thymoglobulin. After 6 months serum creatinine was 1.5mg/dl, c-PRA was 7% class I and he also presented an anti-DQB1*06 with 5106 MFI. He was listed for PAK and received his first pancreas on February-2012. Pancreas mismatch(MM) was 222 and a negative CDC crossmatch was performed. At that time, donor DQB1 typing and virtual crossmatch were not available. There was an hyperacute rejection and pancreas graft was removed immediately. Donor HLA DR was 15,17 and DR 15 may be related to DQB1*06 against which the recipient presented antibody. A second PAK was performed on 2013 after a negative CDC crossmatch and donor ABDRDQ was available only post-transplant showing a respective MM of 0221. After this second PT , recipient c-PRA increased to Class I 37% and patient had an eventful outcome, being insulin-independent until April 2019 when an immunological pancreas loss occurred.

Patient was listed for a third PT in 2014. At that time, his c-PRA increased to 84% Class I and 27% Class II and virtual crossmatch was already available. There were 86 positive crossmatch offers over time and due the challenge for matching this and other recipients , a specific protocol for HS patients was implemented in our team and will be presented. A compatible donor was finally found on July 2021 and a third PT was performed. Virtual crossmatch was negative and donor ABDRDQ MM was 2210 with only a DSA in locus C*06 of 1375 MFI. His outcome was uneventful, rejection-free and patient is doing fine insulin-independent. A DSA monitoring protocol has been performed every 3 months and the C*06 DSA has declined over time.
Conclusions: The use of a more detailed immunologic protocol for better screening and interpreting crossmatch results has proved to be fundamental in these HS patients.

CC04

KIDNEY AUTOTRANSPLANTATION AFTER IPSILATERAL SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANT

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Background: Ipsilateral simultaneous pancreas-kidney transplantation(iSPK) is an attractive surgical strategy once can reduce operative time and preserve or prevent the left fossa to be dissected. We report herein a major complication related to iSPK with an unusual treatment.

Case Report: A 42-year-old man type 1 diabetic since the age of 25 and on hemodialysis for the last 15 months underwent a systemic-duodenal drained iSPK. Donor was an 18-year-old male, with trauma as cause of death and KDPI of 2%. Early post-operative(PO) evolution was uneventful with good kidney and pancreatic function since the beginning. On PO days 13, 21 and 25 a significant and recurrent hematic output through the abdominal drain occurred and sequential emergency laparotomy showed bleeding from polar or main renal graft artery which were repaired. In these three reoperations kidney and pancreas graft showed good appearance and patient remained dialysis-free. Abdominal fluid collections were cultured during reoperations and showed *Pseundomonas* and *Candida*. Antifungal and antibiotic treatment were started and as the kidney graft appearance was normal and patient remained dialysis-free by the time of the third reoperation we decided a last attempt to preserve the graft removing the kidney from the right fossa and implanting on the left fossa. A 6-week cycle of antibiotics and antifungal was completed and patient recovered renal function and has maintained insulin-independent with a serum creatinine of 1.7mg/dl without further readmissions.
Conclusions: iSPK remains controversial as there is some concern that ipsilateral placement of both grafts could jeopardize the distally placed kidney graft and potentially increase the risk of surgical complications. Kidney complication such as bleeding may arise from a more contaminated fossa with pancreatic and duodenal fluids and an unusual treatment through kidney autotransplantation was successfully attempted in this case.

CC05

AN MDT APPROACH TO DETECTION, INVESTIGATION AND TREATMENT OF PANCREAS TRANSPLANT GRAFT DYSFUNCTION

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Background: Pancreas transplant dysfunction is identified by elevations in serum amylase and lipase or an increased blood glucose or HbA1c . It is understood that hyperglycaemia occurs only in the more severe, often irreversible, forms of acute rejection, consequently, in some treatment protocols patients with hyperglycaemia are not candidates for rejection treatment. Moreover, graft failure has classically being defined as the need for insulin therapy. However, in the Igls score, pancreas graft function can be classified as good despite the recipient's need for insulin therapy . Furthermore, there is lack of guidance when there are signs of pancreas graft failure and hyperglycaemia. These cases may benefit from MDT approach.
We present 3 cases of pancreas graft rejection, confirmed by pancreas biopsy, and its treatment determined by MDT (transplant surgeon, nephrologist, diabetologist, radiologist and AP).
Methods: Patients with previous pancreas transplant and increased amylase and lipase or increased HbA1c had CT scan, DSA, pancreas CT scan and pancreas biopsy. Results were discussed in MDT and treatment was arranged.
Results: Case 1: Increased amylase and lipase, HbA1c 4,8%, c-peptide 0.73 nmol/l, creatinine 63 and no new DSAs. Pancreas biopsy showed T cell mediated rejection. Treated with 3 pulses of methylprednisolone and ATG. Amylase and lipase normalised, and glucose control maintained.
Case 2: Normal amylase and lipase but with raised creatinine, HbA1c 6,8%, c-peptide 0.69nmol/l and new DSAs. Pancreas biopsy showed antibody mediated rejection. She received 3 pulses of methylprednisolone and was started on basal insulin. Creatinine improved to baseline and glucose control was maintained.
Case 3: Increased amylase and lipase, HbA1c 7,8%, c-peptide 1.75nmol/l and no new DSAs. Pancreas biopsy showed chronic graft loss. Creatinine improved after catheterisation and enteral drainage conversion was performed. Creatinine improved to baseline and HbA1c improved below 6,5%
Conclusions: MDT approach benefits detection, investigation and treatment of pancreas transplant dysfunction. Patients with hyperglycaemia may benefit from rejection treatment and insulin start may not reflect pancreas graft failure. Further studies in pancreas rejection and its treatment are advised.

POSTER PRESENTATIONS

BASIC SCIENCE – ISLET AND PANCREAS

PP01

BIONIC PANCREAS - THE FIRST RESULTS OF FUNCTIONALITY OF 3D-BIOPRINTED BIONIC TISSUE MODEL TRANSPLANTATION WITH PANCREATIC ISLETS.

Marta Klak*[1;2], Michal Wszola[1;2;3], Andrzej Berman[1;2;3], Anna Filip[2], Anna Kosowska[4], Joanna Olkowska-Truchanowicz[4], Grzegorz Tymicki[2], Tomasz Bryniarski[2], Marta Kołodziejska[2], Tomasz Dobrzanski[1], Dominika Ujazdowska[2], Jarosław Wejman[5], Izabela Uhrynowska-Tyszkiewicz[4], Artur Kamiński[4]

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Background: Tissue engineering is currently on advanced stage of development which gives a possibilities for novel strategy of personal treatment of type 1 diabetes. AIM: In the following study, a bioink based on ECM derived from decellularization of porcine pancreas was applied for 3D bioprinting.
Methods: The SCID (n=60) and BALB (n=20) mice were used as a model for in vivo study. Porcine islets mixed with bioink were printed on extrusion printer and transplanted on studied animals. Effectiveness of transplanted petals with regard of their insulin secretion was evaluated based on glucose and c-peptide concentration in blood samples of studied animals. Thus, animals were divided into three groups: mice with transplanted islet-laden petals, mice with transplanted islets into kidney capsule and untreated mice. Examination of studied parameters took place at four time points during the experiment, at the beginning and on day 7th , 14th and 28th day of experiment.
Results: Group with transplanted petals from day 7th expressed lower mean fasting glucose concentration while compared with untreated group (129 mg/dl, 119 mg/dl, 118 mg/dl vs. 140 mg/dl, 139 mg/dl, 140 mg/dl respectively in 7th, 14th and 28th day post-transplantation; $p<0.001$). Post-surgery transverse section of petals revealed that connective tissue of studied animals surrounded and stabilized transplanted petals. Fibroblasts infiltration over time resulted in the process of new blood vessels formation within the petals. Hence, presented in the study bioink provides a favorable conditions for islets functionality. The bioprinted construct was stable over time. Furthermore, no pathological conditions of studied animals were observed which indicates that bioprinted petals were biocompatible.
Conclusions: Bionic flake transplantation lowered glucose levels significantly

PP02

CHARACTERIZATION OF BETA-CELL HETEROGENEITY TO IMPROVE ISLET CULTURE CONDITIONS FOR XENOTRANSPLANTATIOM

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Background: Transplantation of neonatal porcine islets (NPIs) is a promising tool to cure diabetes mellitus in humans. Prior to transplantation of such a primary cell product, NPIs must be isolated from a donor and matured in vitro. In addition to the tremendous loss of mass during culture, ex-vivo culture conditions severely compromise the cluster-forming cells.
Methods: To improve the islet product, it is necessary to understand the effects of culture on β-cells. Therefore, we examined the transcriptional profiles by single-cell RNA sequencing analysis of β-cells from uncultured/native and cultured NPIs from a neonatal (pn5) and a postweaning-aged donor (pn42).
Results: Uncultured β-cells from neonatal islets showed increased expression profiles for cell metabolism (peptide, amide) and transport (protein, RNA), while after weaning they showed increased levels and a broad spectrum of stress signals. This may indicate that the isolation procedure is more stressful for islets from older donors than for younger ones.
There were fewer differences in stress signaling in cultured islets than in native islets. Subclustering of β-cells revealed many clusters with stress signaling profiles. In cultured islets, β-cells with adhesive signaling were particularly susceptible to stress.
Evaluation of transcripts involved in secretion showed that more endocrine-specific/mature signals were found in cultured β-cells, whereas more general signals were found in native islets β-cells. Culture also increased cluster maturity, as evidenced by more cells expressing higher levels of maturation markers.
Proliferation signaling was also more pronounced in both donor ages after culture.
Conclusions: It was found that there are major changes in β-cell identity and maturity during isolation and in vitro culture.
In this preliminary study, we showed that this includes stress and maturation, but also proliferation.
To decipher the effects of culture in detail, more biological replicates need to be added and deeper analyses performed. This is necessary to provide a better basis for optimizing culture conditions for a good xenogeneic product.

PP03

DECELLULARIZED PANCREATIC TAIL AS A MATRIX FOR ISLET TRANSPLANTATION INTO THE OMENTUM

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Background: The isolation process removes islets from their native environment. We aimed to develop an extracellular matrix (ECM) that could provide a microenvironment for islet survival in an omental flap. The fate of the transplanted islets in the ECM

skeletons was followed in the non-diabetic animals with *in vivo* magnetic resonance imaging (MRI) and *ex vivo* histology and environmental electron microscopy.
Methods: Pancreatic tail of the donor pancreas was decellularized by cannulating the splenic vein. Iron-labeled pancreatic islets were implanted into the ECM skeleton and wrapped into the omentum of the non-diabetic rats. ^{1}H MR imaging was performed using a 4.7T scanner immediately after transplantation into the omentum and on days 1, 7, 21, 35 and 49. A morphological study of the ECM skeletons was realized with an advanced environmental scanning electron microscopy (A-ESEM) and by histological examination.
Results: Decellularization efficiency was confirmed as a significant reduction ($P<0.001$) in double-stranded DNA content. MRI visualized the iron-labeled islets in the repopulated skeletons as distinct hypointense areas immediately after transplantation as well as in the follow-up period. However, though the unambiguous delimitation of the graft within the omental structures was difficult on day 49 due to low specificity of the ^{1}H MRI. A-ESEM verified integration of the islets inside the ECM skeletons. Immediately after placing the islets into the decellularized skeleton through splenic vein, the islets were mostly localized in the vessels, while from the day 21 they appeared partially dispersed in the ECM.
Conclusions: Pancreatic perfusion via the splenic vein provided smaller ECM skeletons facilitating thus their transplantation into the omentum. Multimodal imaging showed that pancreatic islets remained integrated within the pancreatic ECM skeletons for 49 days. Histological evaluations confirmed their viability and sustained insulin production in non-diabetic syngeneic recipients.
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PP04

EFFECT OF PHOTOBIOMODULATION ON THE VIABILITY AND FUNCTIONALITY OF PANCREATIC ISLETS IN VITRO

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Background: Islet transplantation is a treatment option for patients with unstable type 1 diabetes who continue to experience severe hypoglycemia despite optimal insulin therapy. 50% of islets are destroyed at the time of transplantation due to different stresses (ischemia-reperfusion, IBMR). Light absorption in the near infrared range, known as Photobiomodulation (PBM), was shown to have a positive impact on wound healing and cell regeneration in different pathologies (ulcers, Parkinson's disease) but few data are available on the impact of PBM on pancreatic islets.
Methods: We studied the impact of PBM (670nm by LED, 2mw/cm²) on rat islets viability (by confocal microscopy). Rat islets were obtained after digestion of pancreas with collagenase and purification with a discontinuous density gradient. After isolation, islets were exposed to 3 different stresses: 1) substrate deprivation (1.5 hours in

glucose and serum-free medium) or 2) cytokines cocktail (24-hour incubation in the presence of IL1-β 600IU/mL, IFN-γ 6000IU/mL and TNF-α 6000IU/mL) or 3) hypoxia (16 hours, 1% O2), in presence or not of PBM.
Results: Substrate deprivation-induced mortality (25.9 +/- 8.67%, n=12, $p < 0.001$) was reduced if PBM was performed 24h before stress (15.7 +/- 8.34%, n=12, $p < 0.05$) or during stress (16.0 +/- 9.19%, n=9, $p < 0.01$).
Cytokines-induced mortality (34.7 +/- 7.32%, $n = 5$, $p < 0.05$) is reduced if PBM is performed 24 hours before stress (26.9 +/- 4.27, $n = 5$, $p < 0.05$) or during stress (26.7 +/- 4,59, $n = 5$, $p < 0.05$).
Hypoxia-induced mortality (27.3 +/- 11.9, $n = 8$, $p < 0.01$) remained unchanged if PBM was performed during stress (24.2 +/- 11.5, $n = 8$, $p = 0.923$).
Conclusions: Exposure of islets to PBM prior or during cytokine exposure and substrate deprivation increase islet viability. Further experiments will be conducted on human islets to confirm these results. So far, our results suggest that islets exposure to PBM could be transposed in clinic as preconditioning of islet after isolation, before transplantation in order to improve their viability upon transplantation.

PP05

FORMATION OF RE-AGGREGATED NEONATAL PORCINE ISLET CLUSTERS IMPROVES IN VITRO FUNCTION AND TRANSPLANTATION OUTCOME

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Background: Neonatal porcine islet-like cell clusters (NPICCs) are a promising source for islet cell transplantation. Functionality and survival rate of islets after transplantation are crucial factors for treatment of type 1 diabetes.
Methods: We isolated NPICCs from neonatal piglets, dissociated clusters into single cells, and culture on the Sphericalplate 5D™ to form re-aggregated porcine islets (REPIs). We investigated cluster size, cell death by Calcein/PI and Tunnel staining, cellular composition by flow cytometry, and glucose-stimulated insulin secretion (GSIS) in REPIs and NPICCs. We further transplanted various cluster numbers (n=750, 1500, 3000) of REPIs and NPICCs into streptozotocin-induced diabetic NOD-SCID IL2rγ-/- mice. The primary endpoint was the achievement of normoglycemia (random blood glucose <120 mg/dl) after transplantation. Secondary endpoints included intraperitoneal glucose tolerance test (IPGTT) and histological analysis of endocrine cells.
Results: Compared to NPICCs, REPIs had higher homogeneity in size, less cell death, and increased GSIS. REPIs (1500 IEQ) achieved higher normoglycemia rate then NPICCs (1500 IEQ) (33.3% vs. 85.7%, $p < 0.05$). In IPGTT, REPI group revealed better beta-cell function compared to NPICC group (AUC glucose 0-120 min, 6260 ± 305.3 vs. 8073 ± 536.2, $p< 0.01$). The proportions of endocrine and endothelial cells in graft were similar between REPIs and NPICCs.
Conclusions: Generation of cellular aggregates from dissociated NPICCs provides clusters with improved functionality both *in vitro* and *in vivo* as compared to native NPICCs.

PP06

GABA ADMINISTRATION IN VITRO AND IN VIVO TRANSDIFFERENTIATES HUMAN A CELLS INTO INSULIN-SECRETING B CELLS WITH HETEROGENEITY BETWEEN DONORS

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Background: The transplantation of human islets remains a spectacular method that reserved for a privileged few. A treatment against diabetes must be cheap and accessible even to third world countries. **GABA,** identified by molecular screening, induces conversion of **α cells** to **β cells** in murine and human islets. Murine studies have proven to be controversial and only one publication shows an increase in human β cells and plasma insulin levels. The aim is to confirm *in vitro* and *in vivo* the effect of **GABA** on human islets.

Methods: In vitro, 6 human islet preparations were cultured in 3D with or without **GABA** for 15 days or 30 days (n=3 for 30 days). In vivo, 7 human islet preparations transplanted into immunodeficient mice were treated with or without **GABA**, administered daily for 28 days (n=3 mice/conditions) with monitoring of blood glucose, weight and human C-peptide levels. The surface of **Insulin**, **Glucagon** and Chromogranin A was quantified by immunofluorescence.

Results: **GABA** induced a slight conversion of **α cells** to human **β cells** *in vitro* and *in vivo* :

In vitro @14 days: Control 68.91% ± 3.75% vs. **GABA** 74.64% ± 5.39% **β-cells** and Control 31.09% ± 3.75% vs. **GABA** 25.36% ± 5.39% **α cells**.

In vitro @ 28 days: Control 74.95% ± 5.39% vs. **GABA** 79.39% ± 5.55% **β-cells**, and Control 25.05% ± 5.39% vs **GABA** 20.61% ± 5.55% **α cells.**

In vivo @ 30 days: Control 63.04% ± 4.69% versus **GABA** 66.21% ± 5.99% **β-cells** and Control 36.96% ± 4.69% versus **GABA** 33.79% ± 5.99% **α cells** with significant heterogeneity between donors.

In 1 month, **GABA** had no impact on blood glucose, weight and human C-peptide levels (p>0.05).

Heterogeneity of response between donors is represented in the table below :

In vitro 14 days

Donors	% Insulin **Control** vs GABA	% Glucagon **Control** vs GABA
H934	68,77 ± 4,43 vs 87,85 ± 4,04 (+ 19,08%)	31,23 ± 4,43 vs 12,15 ± 4,04 (- 19,08%)
H940	54,49 ± 2,99 vs 61,50 ± 3,27 (+ 7,01%)	45,51 ± 2,99 vs 38,50 ± 3,27(- 7,01%)
H1113	75,39 ± 1,93 vs 84,58 ± 2,41 (+ 9,19%)	24,61 ± 1,93 vs 15,42 ± 2,41 (- 9,19%)
H1121	66,50 ± 2,97 vs 61,68 ± 2,54 (- 4,82%)	33,50 ± 2,97 vs 38,32 ± 2,54 (+5%)
H1124	81,58 + 1,90 vs 87,42 + 1,48 (+ 5,84%)	18,42 + 1,90 vs 12,58 + 1,48 (- 5,84%)
H1161 (Diabetic)	66,72 + 3,75 vs 64,84 + 2,73 (-1,88%)	33,28 + 3,75 vs 35,16 + 2,73 (+ 1,88%)

In vitro 28 days

Donors	% Insulin **Control** vs GABA	% Glucagon **Control** vs GABA
H1113	65,31 + 2,47 vs 68,39 + 2,36 (+ 3,07%)	34,69 + 2,47 vs 31,61 + 2,36 (- 3,07%)
H1121	75,60 + 2,05 vs 83,66 + 1,44 (+ 8,07%)	24,40 + 2,05 vs 16,34 + 1,44 (- 8,07%)
H1124	83,95 + 1,82 vs 86,12 + 2,18 (+ 2,17%)	16,05 + 1,82 vs 13,88 + 2,18 (- 2,17%)

In vivo

Donors	% Insulin **Control** vs GABA	% Glucagon **Control** vs GABA
H833	42,78 ± 2,62 vs 38,51 ± 1,72 (- 4,27%)	57,22 ± 2,62 vs 61,49 ± 1,72 (+ 4,27%)
H843	70,60 ± 1,23 vs 77,62 ± 1,31 (+ 7,02%)	29,40 ± 1,23 vs 22,38 ± 1,31 (-7,02%)
H1111	57,58 ± 1,94 vs 64,70 ± 3,38 (+7,12%)	42,42 ± 1,94 vs 35,50 ± 3,38 (-7,12%)
H1112	51,76 ± 1,84 vs 52,26 ± 1,80 (+ 0,50%)	48,24 ± 1,84 vs 47,44 ± 1,80 (+ 0,50%)
H1113	74,05 ± 1,06 vs 79,47 ± 1,26 (+ 5,44%)	25,95 ± 1,06 vs 20,53 ± 1,26 (- 5,44%)
H1119	74,10 ± 1,21 vs 81,20 ± 0,97 (+ 7,11%)	25,90 ± 1,21 vs 18,80 ± 0,97 (- 7,11%)
H1121	70,44 ± 1,64 vs 69,72 ± 1,08 (- 0,72%)	29,56 ± 1,64 vs 30,28 ± 1,08 (+ 0,72%)

Conclusions: **GABA** is able within 1 month of time to induce a concomitant decrease in human **α cells**, and an increase in **β cells** and enhance NKX6.1 expression. The heterogeneity of responses between donors may be linked to variable **α-cells** subpopulations. More studies with human islets are needed to detect whether **GABA** will be promising as a future treatment for islet transplant recipients and diabetic patients in general.

PP07

GENERATION AND CHARACTERIZATION OF PORCINE DERIVED PSEUDO-ISLETS FOR ISLET CELLS REPLACEMENT

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Background: Pancreatic islet transplantation is a safe and minimally invasive curative treatment option for patients with insulin-dependent diabetes. However, the availability of this treatment remains limited due to the need for immunosuppression and the shortage of donors. To overcome these limitations, our group has developed immune-shielding strategies for islet macro-encapsulation [1] and exploited the utilization of alternative cell sources such as xenogeneic adult and neonatal pig islets [2]. In the macro-encapsulation setting, it is essential to use intact uniform islets with high purity and ideal size in order to reduce oxygen demand, maximize applicable density, and obtain optimal diffusion characteristics. This can be achieved by Pseudo-islets (PIs) system. However, unlike other species, porcine islets fail to form PIs due to differences in basement membrane compositions [3]. Here, we managed to overcome

this issue and establish a reproducible protocol of PIs generation from both adult pig and neonatal pig islets-cells like clusters (pNICCs). We further fully characterized the generated PIs morphology, viability, functionality, transcriptomics and glucose metabolic flux analysis in comparison to native islets.

PP08

HYDROGEL-BASED, PREVASCULARIZED, RETRIEVABLE ENDOCRINE CONSTRUCT TO TREAT TYPE 1 DIABETES

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Background: The goal of our study was to generate a functional, prevascularized endocrine constructs utilizing amniotic membrane derived hydrogel, islets and blood outgrowth endothelial cells (BOECs) to be transplanted in diabetic hosts.
Methods Human amniotic membranes were dissected from placentas decellularized, lyophilized, and solubilized to obtain hydrogels. To study the impact of generated gels on islet function in vitro, both rodent and human derived islets and human derived blood outgrowth endothelial cells were admixed in hydrogels and cultured in vasculogenic media to enhance endothelial cell assembly into tubular, vascular-like structures. To test in vivo biocompatibility and function, the vascularized constructs generated from 500 IEQ rat islets and 2×10^5 BOECs were implanted under the skin of the diabetic NSG mice.
Results: Engineered vascularized constructs supported islet function, and development of an abundant vascular network well integrated with islets. Blood glucose levels of the mice transplanted with vascularized constructs normalized rapidly and normoglycemia was maintained long-term. Histological analysis of the explanted grafts revealed healthy islet morphology and perfect revascularization. The experiments replicated utilizing human islets had similar outcomes as it's demonstrated on this chart, we observed rapid increase of human C-peptide in the mice after transplantation. Explanted grafts displayed excellent islet morphology, hormone expression and most importantly intense vascularization. Presence of red blood cells within the capillaries in the graft area and positive alpha SMA staining indicated that that vessels inside the graft were functional and fully matured.
Conclusions: Our findings show that amnion derived hydrogel seeded with endocrine pancreatic tissue and endothelial cells could be used for functional, preveascularized endocrine construct bioengineering.
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PP09

IMPACT OF HYPOTHERMIC PERFUSION ON ENDOTHELIAL FUNCTION IN A PRE-CLINICAL MODEL OF PANCREATIC TRANSPLANTATION

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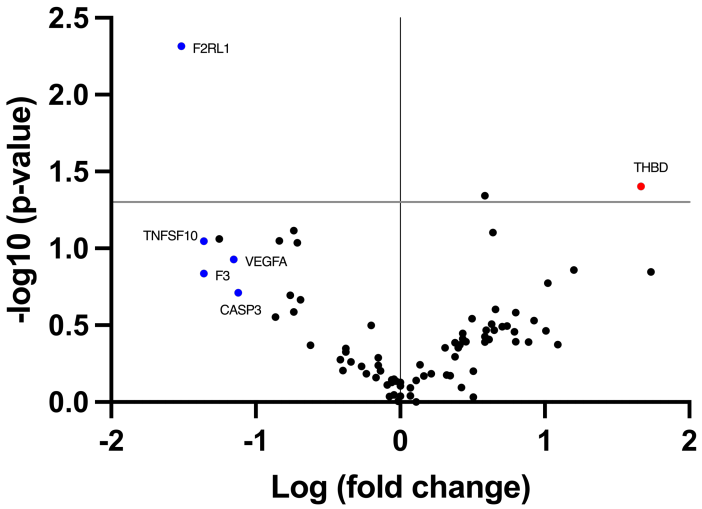
Background: Oxygenated hypothermic perfusion (HOPE) is currently under investigation in kidney and liver transplantation to improve the safety and outcomes of transplantation from marginal donors. The effect of HOPE on endothelial function has been poorly evaluated in organ transplantation. We propose to evaluate the effect of HOPE on endothelial function in a pre-clinical model of pancreatic transplantation.
Methods: We set up a porcine donation after circulatory death model (warm ischaemia:). After procurement, pancreases were preserved during 24 hours in hypothermic condition either in statical condition (n=4) or on HOPE (n=4) (Waves machine, Georges Lopez Institute, 100% oxygenation at 2L/min). Surgical biopsies were performed after organ procurement and after 3 and 24 hours of preservation. The differential expression of markers of endothelial function between the 2 preservation modalities was assessed by quantitative RT-PCR (RT-Profiler PCR Array, Qiagen). The expression of 84 genes involved in endothelial physiology was assessed.
Results: The analysis of the associated markers of vascular endothelial function expression highlighted an overexpression of markers of inflammation, cell adhesion, and apoptosis during static preservation for 3 h and up to 24 h of preservation. In contrast, a decrease in markers of antithrombotic activity was observed during statical preservation (THBD). Comparison of gene expression during static preservation and HOPE suggests a decrease in the expression of several genes involved in inflammation (IL-6, F2RL-1, TNFS10, F3), apoptosis (CASP3, EDNRA), or related to ischemia (VEGFA), associated with an increase in the expression of genes related to vasodilation and anticoagulant effect (THBD). (Figure 1.)

Conclusions: Our results suggest that HOPE may influence endothelial cell biology during preservation by decreasing markers related to inflammation and apoptosis.

Figure 1

Endothelial cell gene expression

Group test : Hypothermic oxygenated machine perfusion
Group control : Statical cold storage



PP10

IMPLANTATION OF ISLET DELIVERY DEVICE IN SUBCUTANEOUS HIGH FRICTION SITES IN A PORCINE MODEL RESULT IN SIGNIFICANT FOREIGN BODY RESPONSE

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Background: Islet delivery devices can potentially mitigate the loss of donor islets by implantation into extrahepatic sites. A previously reported open microwell islet delivery device, which was shown to lead to normoglycemia in diabetic mice, was further developed for future clinical translation. In a previous experiment, we demonstrated safe loading and transportation of the device with pancreatic islets. Since many implantation sites are still being debated, we now investigated the effect of low friction versus high friction subcutaneous implantation sites on engraftment of the microwell delivery device.

Methods: Oval-shaped 27 x 44 mm thin film islet delivery devices were manufactured from GMP grade polyvinylidene fluoride using a combination of microthermoforming and laser micromachining. In 4 immunocompetent Landrace pigs, we implanted 18 empty devices and performed 4 sham operations subcutaneously in the neck (high

friction site) and abdomen (low friction site). After 3 months, all remaining devices were retrieved. Porcine tissue response and device microstructure were evaluated.
Results: All subcutaneous pockets were pre-fitted with a dummy device to confirm adequate size. Standard surgical instruments were used to implant all devices. No complications occurred during implantation or retrieval after 3 months. Post-retrieval evaluation showed that devices were not broken and had retained their microwell structure. In all devices, tissue ingrowth could be seen with fine bands of connective tissue and well-established vascular channels. Devices implanted in the neck site showed an increased foreign body response compared devices in the abdominal site in 3 pigs. In the high friction sites, 2/8 devices were lost, compared to 0/7 in the low friction sites. One pig with 3 devices died shortly after implantation due to a heart condition. These devices were not analyzed.
Conclusions: PVDF islet delivery devices can safely be implanted and retrieved in pigs. High friction sites for subcutaneous implantation these devices are likely to pose a higher risk for device damage or loss.

PP11

INHIBITION OF NETOSIS PREVENTS DYSMETABOLISM AND PRESERVE GLP-1 PRODUCTION. A POSSIBLE ROLE IN PROTECTING ISLETS FUNCTION.

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Background: Obesity and type 2 diabetes rewire the immune system leading to a chronic low-grade inflammatory tone, which fuels insulin resistance and compromises β-cell function. In parallel, diabetes promotes metabolic endotoxemia, intestinal permeability and dysbiosis. The role neutrophils in the development of obesity and insulin resistance has been largely neglected. Diabetes prime neutrophils to release neutrophil extracellular traps (NETs) composed of granular proteins/enzymes and nuclear material while the microbiota can modulate NETosis. We aim to investigate whether neutrophils could bridge the effects of dysbiosis toward systemic metabolism.
Methods: We generated a hematopoietic restricted Padi4 knock-out mouse. Padi4KO and Floxed mice were assigned to a standard diet (STD) or a high fat diet (HFD) for 12 weeks before performing metabolic characterization, histological analysis and microbiota phenotyping. We have also evaluated intestinal permeability, plasma LPS, circulating metabolic hormones and inflammation.
Results: The deletion of *Padi4* prevented histone citrullination and NETs release *in vitro*. Padi4KO mice were protected from the surge of circulating dsDNA induced by the HFD, a canonical biomarker of NETosis, and systemic inflammation. *Padi4* deletion had no effect on weight gain due to HFD but Padi4KO mice were more glucose tolerant and less insulin resistant compared to Floxed mice. Padi4KO mice were also protected by the decline in GLP-1 levels after HFD. We found that islet hypertrophy associated with HFD was reduced in Padi4KO mice. HOMA-IR values confirmed the protection of Padi4KO mice from insulin resistance. Accordingly, Floxed mice were hyperinsulinemic and their insulin/glucagon ratio was increased by fourfold. Padi4KO

mice were protected from intestinal hyperpermeability and from the surge of circulating LPS induced by the HFD, despite the onset of dysbiosis.
Conclusions: We show that NETosis is involved in the development of dysmetabolism, sensing the onset of dysbiosis and propagating inflammation. Our preliminary data pinpoint that preventing NETosis could protect islets possibly through preserved GLP-1 production and reduced inflammation. Thus, the interplay between NETosis and islets homeostasis in type 2 diabetes is worthy exploring in future studies.

PP12

MATURATION AND EVALUATION OF 3D PRINTED BIONIC PANCREAS WITH A DEDICATED BIOREACTOR

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Background: The technology of 3D printing of bionic organs gives an opportunity to solve the problems of classical transplantology, such as the shortage of organs, complications of immunosuppression or rejection. After printing, the bionic pancreas requires an optimal environment conditioning the process of its maturation, which consists in the colonization of the produced vessels with endothelial cells and the tubularization of the endothelium within the microcirculation. After the maturation process is completed, it is necessary to evaluate the resulting organ in terms of its functionality and safety.
Methods: In order to minimize the risk of contamination while ensuring the necessary functionalities, a bioreactor was created that allows the maturation of the bionic pancreas, and after the end of the process, functional assessment using the semi-automatic Glucose-Stimulated Insulin Secretion (GSIS) test and the assessment of vascular tightness using the pressure test. 10 procedures of maturation and bionic pancreas evaluation were performed using a bioreactor. 5 pancreas contained human beta cells and 5 pancreas contained porcian isolated pancreatic islets. The mean pancreatic maturation time was 23 hours (2-72 hours). The effectiveness of adhesion of endothelial cells to the vascular wall and tubularization of endothelial cells was assessed by immunohistochemistry. The GSIS test was performed by automatically replacing the medium with glucose at various concentrations. The integrity of the vascular system was assessed by maintaining a pressure of 190 mmHg for 5 minutes.
Results: The adhesion of endothelial cells to the bioink was observed after 1 hour. Tubularization of the endothelium was observed after 48 hours. Insulin secretion upon GSIS was observed without delay to the control and the insulin concentration during the observation showed a constant ratio compared to the control, but without a clear peak at high glucose concentration. In 8 out of 10 pancreas, no vascular leakage was observed during the pressure test.
Conclusions: The use of a dedicated bioreactor enables safety during the bionic maturation process of the organ, while allowing for an effective assessment of the organ's functionality and the tightness of the vascular system.

PP13

NORMOTHERMIC PERFUSION, AN INNOVATIVE METHOD TO EVALUATE PANCREATIC TRANSPLANTS?

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Background: To date, there are few markers available to predict early function of pancreatic grafts. Ex-situ normothermic perfusion appears to be a method of interest for this purpose. Here we report on the development of normothermic perfusion in a preclinical porcine model and then in a non-human primate and finally in a preclinical human model.

Methods: The normothermic perfusion device is derived from a paediatric extracorporeal circulation (Sorin Group, LivaNova, London, UK). It consists of an organ chamber that acts as a venous reservoir, a centrifugal pump, an oxygenation membrane and a heater. The perfusion solution consists of leukoreduced whole blood obtained from the donor. The perfusion was performed at 40 mmHG, 37°C and with oxygenation at 1L/minute (95% oxygen). Pancreases were perfused for 2 to 6 hours.

Results: Ex-situ normothermic perfusion was successively achieve in all models. The resistance index, arterial flow, temperature, and intra-tissue partial pressure of oxygen seem to be important markers of satisfactory tissue perfusion. An assessment of the revascularisation is also possible by innovative imaging modalities and in particular by photoacoustics. Exocrine suffering can be assessed by measuring blood lipase and amylase levels. Exocrine function can be approximated by collecting pancreatic and duodenal secretions (volume, appearance, biochemistry). Endocrine function can be assessed by glucose stimulation tests.

Conclusions: Ex-situ Normothermic perfusion is feasible in any model and could predict the function of pancreatic transplants prior to transplantation. It also appears to be an innovative method of preconditioning transplants.

PP14

OPTIMISATION OF A NOVEL SUSPENSION MICROCAVITY SYSTEM FOR VIABLE, FASTER AND MORE UNIFORM GENERATION OF PSEUDO-ISLETS FOR TYPE 1 DIABETES RESEARCH

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Background: Reduced viability *in vitro* and worse clinical transplant outcomes have been reported for deceased donor pancreatic islet isolations with mean diameter >150

μm[1]. We aimed to evaluate the use of novel 3D microcavity suspension-well plates for rapid generation of viable optimally sized pseudo-islets.

Methods: We utilised a microcavity suspension culture system (SphericalPlate 5D (SP5D), Kugelmeiers Ltd., Erlenbach, Switzerland). Each well contains 750 microcavities. MIN6 murine β-cells were seeded at low to high densities (75,000; 187,500; 300,000; 412,500; 525,000; 637,500 (cells/well)) into SP5D and control 24-well suspension plates (CS) and cultured at 37°C with pseudo-islet diameter assessed using an eyepiece graticule and visual estimation of viability assessed using propidium iodide staining at Day 3 (D3) and Day 5 (D5).

Results: Optimal seeding density for SP5D plates was determined to be 525,000 cells/well in initial 3 days culture studies (Table 1). In comparison to CS wells, optimally sized pseudo-islets were generated more rapidly in SP5D so that at D3, diameter size was significantly higher (SP5D: 97.2 ± 9.2; CS: 72.5 ± 31.1; p=0.02; n=3 mean ± SD (μm)) with comparable viability (SP5D: 77.8 ± 12.4; CS: 76.1 ± 13.6; p=0.9; n=3 mean ± SD (%)). A comparison of the standard deviations in diameter size in three repeated studies demonstrated less variability and higher consistency in SP5D than CS (n=3 mean ± SD SP5D: 9.2 ± 3.9; CS: 31.1 ± 4.1; p=0.003). Pseudo-islets with more uniform, spherical morphology were observed in SP5D (Figure 1).

Conclusions: Optimal seeding density yielding rapid generation over 3 days of pseudo-islets <150 μm with viability >70% has been determined. Pseudo-islets of more consistent size and uniform shape over a shorter culture time are generated in this system. Plate loading of the novel plates was straightforward, generating a single pseudo-islet per cavity. Optimisation of the dissociation and reaggregation of isolated human islets into these novel plates with potential clinical translation is ongoing.

[1]Lehmann, R, Superiority of small islets in human islet transplantation. Diabetes. 2007 Mar

SP5D DAY 3 DATA		
Seeding Density (cells/well)	Diameter (μm)	Viability (%)
75,000	23.8 ± 14.3	96 ± 12.8
187,500	65 ± 19.6	78.6 ± 19.7
300,000	92 ± 20.9	72.1 ± 15.4
412,500	83.6 ± 18.6	72.4 ± 13.7
525,000	92.4 ± 19.1	82.8 ± 16.7
637,500	93.8 ± 12.4	71.5 ± 16.7
	p<0.001	p<0.001

Table 1: Day 3 assessment of diameter and viability of pseudo-islets cultured in SphericalPlate 5D (SP5D).
Data are mean ± SD (n=50 pseudo-islets). Means compared by one-way ANOVA.

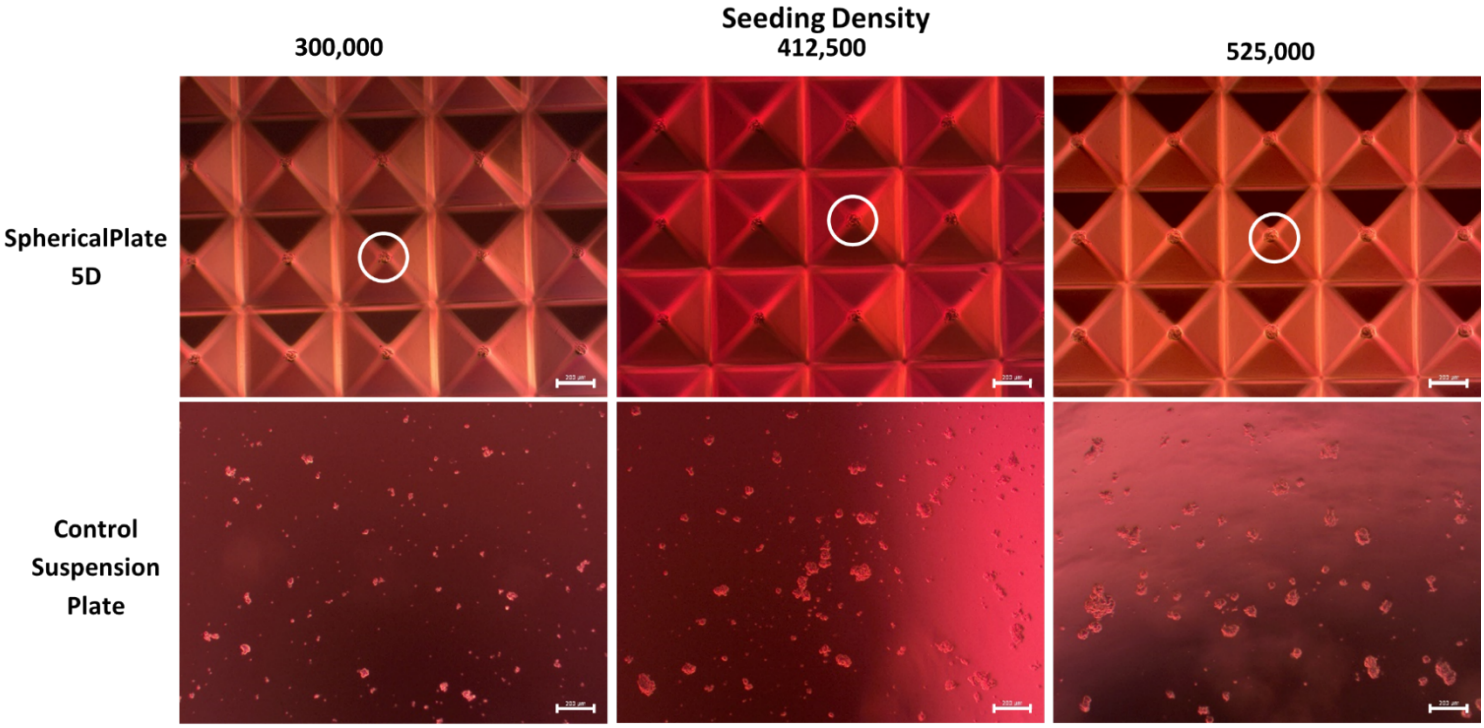

Figure 1: D3 pseudo-islet morphology at different seeding densities in SphericalPlate 5D (SP5D) and control suspension wells (CS). SP5D generates more consistent and spherical pseudo-islets than CS. 525,000 was determined as the optimal seeding density in SP5D. White circles indicate one pseudo-islet in one SP5D microcavity. Brightfield images were taken using the Zeiss Axiovert 200M inverted microscope. 5x magnification, scale bar = 200 µm.

PP15

OPTIMISATION OF TISSUE OXYGENATION DURING PRESERVATION BY HYPOTHERMIC PERFUSION IN A PRE-CLINICAL MODEL OF PANCREATIC TRANSPLANTATION

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Background: Pancreatic transplants from marginal donors are increasing. Perfusion improves the preservation of kidney and liver transplants. We propose to evaluate the effect of hypothermic oxygenated perfusion more or less associated with an M101 oxygen carrier on in-tissue partial pressure of oxygen.

Methods: We set up a pre-clinical donation after circulatory death porcine model (warm ischemia: 30 minutes). After organ procurement, pancreas were preserved for 24 hours in hypothermic condition either in statical storage (n=8) or on hypothermic machine perfusion (HMP) (n=24) (Waves machine, Institut Georges Lopez) associated or not with oxygenation (21% or 100%, 2L/min). The addition of an oxygen carrier (M101, Hémarina) was also evaluated. The in-tissue partial pressure of oxygen was assessed by probes implanted in the parenchyma.

Results: The in-tissue partial pressure of oxygen decreased during statical cold storage to 0 after 2 hours. During HMP, the in-tissue partial pressure of oxygen increased during the first 2 hours before stabilising. Hypothermic perfusion without the addition of oxygen was an efficient modality to provide oxygen to the parenchyma. HOPE with 100% oxygen corresponded to a situation of hyperoxia. In parallel, the resistance index decreased during the first 2 hours before stabilising. There was a correlation between in-tissue partial pressure of oxygen and resistance index. The addition of an oxygen carrier did not influence the in-tissue partial pressure of oxygen.
Conclusions: Hypothermic perfusion, whether oxygenated or not, appeared to be an effective preservation modality to provide oxygen to pancreatic grafts. The evaluation of the oxygenation-resistance index correlation would allow the establishment of perfusion targets adapted to each graft.

PP16

PANCREATIC ISLETS TRANSPLANTED IN A DECELLULARIZED PANCREATIC MATRIX – EFFECT OF MESENCHYMAL STEM CELL

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Background: Mesenchymal stem cells (MSCs) support tissue regeneration, suppress immune response and promote angiogenesis. We studied the ability of MSCs alone or together with endothelial cells (ECs) to promote vascularization of rat pancreatic islets transplanted into decellularized pancreatic matrix (pECM). We tested also the immunomodulatory ability of MSCs.
Methods: We tested the immunomodulatory effect of MSCs in vitro and in vivo. Using modified mixed lymphocyte reaction (MLR) we studied the ability of rat MSCs to reduce the reactivity of rat splenocytes to non-specific phytohemagglutinin (PHA) stimulus and to human ECs in vitro. In vivo, we transplanted xenogeneic human green fluorescent protein-expressing ECs alone or together with MSCs under the rat kidney capsule.
In the next step, rat pancreatic islets were transplanted into pECM subcutaneously in a syngeneic model. The islets were infused into the matrix A) alone, B) in combination with MSCs, and C) in combination with both MSCs and syngeneic ECs. 9 days after transplantation, the grafts were excised and islet vascularity was tested using anti-CD31 antibody staining.
Results: In vitro, the presence of MSCs reduced the proliferation of splenocytes as a response to PHA and human ECs were reduced by 47 % and 58 %, respectively ($p<0.05$).
Despite this effect in vitro, in vivo the MSCs did not prevent rejection of the GFP-expressing ECs. In groups A and C, revascularization of the grafts was poor. In contrast, in group B (pancreatic islets together with MSCs), the vascularity of the grafts was sufficient to enable islet survival.
Conclusions: In vitro, MSCs reduce the immune response of splenocytes to xenogeneic ECs. However, the immunomodulation of locally transplanted MSCs was not sufficient to suppress the post-transplantation immune response to xenogeneic ECs. A positive effect on vascularization of decellularized matrices was achieved only by addition MSCs without ECs co-transplantation.
Acknowledgment: Funded by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, Project No. LX22NPO5104) -

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PP17

PRE-CONDITIONING OF TRANSPLANTS ON A HYPOTHERMIC PERFUSION MACHINE IN A PRE-CLINICAL MODEL OF PANCREATIC TRANSPLANTATION

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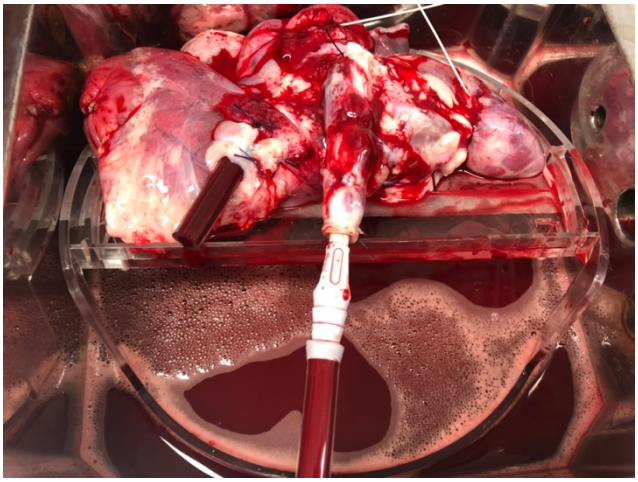
Background: Pancreatic transplants from marginal donors (expanded criteria donors or donation after circulatory death (DCD)) are increasing. Hypothermic perfusion improves preservation of kidney and liver grafts. We propose to evaluate the effect of hypothermic perfusion on the revascularisation of pancreatic grafts during transplantation.

Methods: We set up a pre-clinical porcine model (n=40) of DCD donor (warm ischemia: 30 minutes). After procurement, pancreases were preserved during 24 hours in hypothermic condition either in statical storage (n=8) or on a hypothermic machine perfusion (HMP) (n=24) (Waves machine, Institut Georges Lopez) associated or not with oxygenation (21% or 100%, 2L/min). After 24 hours of preservation in hypothermic condition, pancreatic grafts were re-perfused thanks to an ex-situ normothermic perfusion device derived from a paediatric extracorporeal circulation (Figure 1.). A validation of the previously obtained results was then performed on a short preservation time (2 hours) (n=8).

Results: Pancreases preserved on a HMP had lower resistance during reperfusion associated with better perfusion rate than pancreases preserved in statical cold storage. This decrease in resistance index was associated with an improved oxygen delivery during reperfusion. There was no impact of oxygenation during hyporthermic preservation on resistance and oxygenation levels during reperfusion. A short preservation period (2 hours) confirmed these data.

Conclusions: Preservation of pancreatic transplants on HMP condition grafts for reperfusion. Vessel preparation allows for better vascularisation (i.e. oxygenation) during grafts' revascularisation.



PP18

SOLUBILIZED EXTRACELLULAR MATRIX EXTRACTED FROM PORCINE PANCREASES PROTECTS HYPOXIA-EXPOSED ISOLATED HUMAN ISLETS

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Background: Previous studies suggest that individual extracellular matrix (ECM) proteins can increase the survival of isolated islets. Nevertheless, the natural ECM is a highly complex protein network. We therefore pursued the development of a more physiological islet matrix by extracting the ECM from pancreases of juvenile pigs (ppECM) and compared it to a pretested mixture of human collagen-IV + laminin-521 + nidogen-1 (hEPM). In contrast to previous studies, ppECM and hEPM were dissolved in media rather than coating culture surfaces.

Methods: Isolated human islets (n = 8) were suspended in CMRL supplemented with 180 µg/mL ppECM or 120 µg/mL hEPM and cultured for 4 – 5 days in hypoxia. Culture without addition of ECM components served as sham-treatment (SMT). Characterisation included yield of IEQ and islet number (IN), viability (FDA-PI), apoptosis (annexin V-PI), glucose stimulation index (SI: 2 vs 20 vs 2 mM), production of reactive oxygen species (ROS) (DCFH-DA) and TNF-α. Parameters were related to IEQ and normalised to preculture data (mean ± SEM).

Results: Recovery was lowest when islets were treated by SMT (41 ± 7%) and compared with hEPM (57 ± 5%, $p<0.05$) or ppECM (72 ± 8%, $p<0.001$). Islet fragmentation (IN/IEQ ratio) was increased in SMT (1.04 ± 0.20) compared with hEPM (0.78 ± 0.10, NS) or ppECM (0.58 ± 0.06, $p<0.05$). Initial viability was preserved when hEPM (vs 93 ± 7%, $p<0.05$ vs SMT) or ppECM (101 ± 8%, $p<0.001$) were used but not after SMT (79 ± 8%, $p<0.01$). Initial ROS production triplicated after SMT (298 ± 42%) but remained low in the presence of hEPM (132 ± 13%, $p<0.05$) or ppECM (120 ± 12%, $p<0.001$). TNF-α release doubled after SMT (1.58 ± 0.09 ng/IEQ) when compared with hEPM (0.86 ± 0.17, $p<0.05$) or ppECM (0.82 ± 0.17, $p<0.01$). Initial apoptosis remained stable when islets were treated with hEPM (93 ± 8%) or ppECM (91 ± 9%), but rose after SMT (143 ± 8%, $p<0.01$). SMT-islets did not respond adequately to glucose (0.86 ± 0.1 SI) in contrast to hEPM- (1.32 ± 0.07, $p<0.05$) or ppECM-islets (1.47 ± 0.12, $p<0.001$).

Conclusions: Our study shows that solubilized ECM extracted from pancreases of juvenile pigs is highly efficient to protect human islets from hypoxia-induced damage. This finding may serve as starting point for improved culture and encapsulation techniques.

PP19

SUCCESSFUL 3D BIOPRINTING OF PRIMARY ISLETS AND BETA CELLS DEPENDS PRIMARILY ON THE DIFFUSION KINETICS OF THE HYDROGEL USED

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Background: Intrahepatic clinical islet transplantation (CIT) is currently the only cell therapy available to treat severe cases of type 1 diabetes, but the liver is a suboptimal implantation site. 3D bioprinting, is a technique allowing one to create hydrogel-based implants at ambient conditions while cells are deposited at the same time potentially combining the advantages of macro- and microencapsulation in one cell delivery device. We report on the systematic analysis of different alginate hydrogel formulations for 3D bioprinting of islets using fluorescent recovery after photobleaching (FRAP) and hydrogel mesh size measurements to determine the exchange of nutrients and insulin to and from the islets. The selected 1.5% alginate was used to bioprint INS1E cells, primary rat, and human islets.
Methods: FITC-labeled dextrans, 3-5 kDa, 10 kDa, 20 kDa or 70 kDa, were used to determine the diffusion properties of different alginate formulations, 1.5%, 2.0%, 2.5% and a 4% alginate-5% gelatin mixture by FRAP. The mesh size was determined using a rheometer. Based on results from rheology and FRAP the most optimal alginate formulation was selected to bioprint primary rat and human islets in Ø10 mm discs for analysis of beta cell function and viability.
Results: FRAP showed that in all hydrogels the diffusion constant increased when moiety size was smaller, which was highest in the 1.5% alginate formulation, with an apparent diffusion of 132 ± 3, 184 ± 11, 221 ± 20 and 274 ± 12 $\mu m^2/s$ for 70, 20, 10 and 3-5 kDa dextrans respectively. Rheology revealed that 1.5% alginate hydrogel has a significantly lower storage modulus, 4.7 ± 0.7 kPa, and a significantly higher mesh size, 11.9 ± 0.6 nm compared to all other hydrogel formulations. Bioprinted INS1E cells, rat islets and human islets showed ~85% viability and good endocrine function albeit lower insulin secretion then controls.
Conclusions: We showed that 1.5% ultrapure alginate is the most optimal hydrogel formulation for 3D bioprinting of islets. We recommend that one uses the methodology presented to determine suitability of a hydrogel for 3D bioprinting of islets.

PP20

TOWARDS A CELL BASED ISLET DELIVERY

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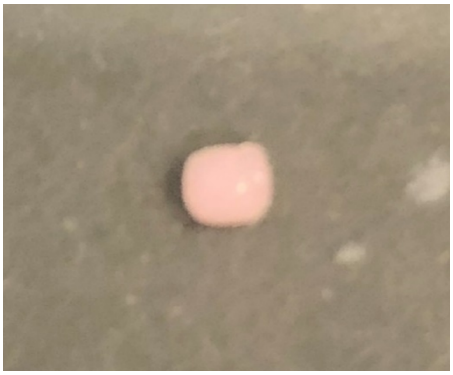
Background: During the isolation process for clinical islet transplantation the extracellular matrix and microvasculature of islets are destroyed leading to poor engraftment and significant loss of transplanted cells. Over the last years, alternative methods have been proposed to create a better environment for islets and improve survivability and function. Most of these strategies are based on biomaterials, which, eventhough biocompatible, will cause a foreign body response and scar tissue around the implant. Here we are showing two cell based apporaches that are aiming to create a more natural environment for islets.
Methods: Cell sheets of immortalized mesenchymal stem cells (iMSCs) were cultured on 35 mm thermoresponsive NUNC UpCell dishes. Multiple cell sheets were layered on top of each other to encapsulate human donor islets. The function of human islets was measured with a static glucose stimulated insulin secretion assay. iMSCs and HUVECs were coculture to achieve vascular like structures on cell sheets. CD31 staining was used to visualize possible vascular like structures.

iMSCs were cultured into aggregates and seeded into a commercially available net mold to grow tissue cubes of varying sizes. PreSens Oxy10 system was used to measure the oxygen concentration inside the cube.

Results: After optimization, it was possible to stack up to four cell sheets and still handle them without rupturing them. Human islets encapsulated between two bottom and two top cells sheets showed functionality, indicating no impaired diffusion. Coculturing HUVECs with iMSCs resulted in a vascular mimicking network in cell sheets.

Through optimized cell culture cubes of different sizes were grown. Oxygen measurements under normal culture condition showed hypoxia in the middle of the cube.



1x1x1 mm iMSC cell cube

Conclusions: Here we introduced two completely cell based approaches to create a better-suited environment for islets. Islets inside cell sheets are responsive to glucose and secrete insulin. Cell sheets with vascular mimicking networks were grown which could help with vascularization when implanting. It was possible to grow small tissue cubes. Both approaches could be tailored to be patient specific and it might be possible to combine them with iPSC derived beta cells in the future.

CLINICAL: ISLET

PP21

ISLET AFTER KIDNEY TRANSPLANTATION IN TYPE 1 DIABETES PATIENT: FIRST EXPERIENCE IN BALTIC COUNTRIES

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Background: Islet transplant offers a minimally invasive option for β cell replacement in the treatment of type 1 diabetes (T1DM). The main islet after kidney transplantation (IAKT) goal is to eliminate hypoglycaemia events and restore hypoglycaemia awareness in patients with diabetes. We are presenting case of the first IAKT in Baltic countries performed at Vilnius University hospital Santaros Klinikos.

Case report: 59-year-old male had T1DM since the 16 years of age. Due to poor glucose control he developed diabetic nephropathy which led to the end stage kidney disease. Haemodialysis was started in 1996, kidney transplantation from a deceased donor was performed in 2005. Hypoglycaemia events 4-5 times/week at least twice requiring glucagon injection and hypoglycaemia unawareness were main criteria for IAKT. IAKT of 7000 iE/kg (total of 400,000 iE) from deceased donor was successfully performed on the 3rd of Nov 2021 in co-operation with The Nordic Network For Clinical Islet Transplantation (Uppsala and Stockholm). On November 2nd Uppsala lab got the pancreas organ from Vilnius for isolation which yielded approximately 400 000 IEQ of

good clinical grade islets. A surgeon and a nurse from Sweden went with the islets to Vilnius as courier and to assist on the islet transplantation.
Results: At first there were episodes of glucose fluctuation within the range of 3-14 mmol/l, however no severe hypoglycaemia episodes were registered. Currently hypoglycaemia occurs less often than before IAKT, the patient is aware of hypoglycaemia at plasma glucose of 2,5-2,8 mmol/l. There is a reduction of C-peptide concentration, although HbA1c remains stable. Kidney function, assessed by eGFR, remained stable - eGFR 95 mL/min/1.73 m2 before transplantation and 97 mL/min/1.73 m2 at day 358.
Conclusions: IAKT showed to be a safe procedure for kidney transplant patients with T1DM, already receiving immunosuppression to prevent rejection of transplanted kidney. As a minimally invasive procedure, it is a safe method of treatment with a low risk of complications. IAKT proved to be effective in reducing the number of severe hypoglycaemic events and restoring the hypoglycaemia awareness. Although C-peptide is still traceable, re-transplantation could be considered to ensure long lasting result and possible insulin independence.

PP22

DEVELOPMENT OF AN ADVANCED MACROENCAPSULATION STRATEGY FOR THE TREATMENT OF PATIENTS WITH DIABETES MELLITUS

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Background: Macroencapsulation of porcine islets represents a promising approach for the treatment of patients with insulin-deficient diabetes mellitus. In the present work, an advanced modular device was designed to overcome main hurdles of the currently existing encapsulation systems. The key components of the proposed device include a bioactive immune-isolating membrane and a tailored islet-supporting matrix, as well as an intrinsic oxygen generating module that allows to maintain the viability of the graft in the early post-transplantation period.
Methods: StarPEG-glycosaminoglycan (GAG) biohybrid hydrogels were used to mimic the extracellular matrix environment (ECM) in the islet module of the macroencapsulation device. The viability and functionality of the neonatal porcine islet-like cell clusters (NICCs) pseudoislets embedded in starPEG-heparin and alginate hydrogels were assessed with FDA-PI staining, glucose-stimulated insulin secretion (GSIS), and antibody staining. With the application of 3D-printing and PDMS molding techniques the oxygen-generating disks (PDMS-CaO_2) were manufactured in accordance to the dimensions of the device. The disks were characterized with regards to their oxygen release profile and utilizing staining and microscopy techniques. To estimate the overall oxygen availability in the islet macroencapsulation device, oxygen diffusion was simulated by “COMSOL Multiphysics” software.
Results:

- The NICCs pseudoislets embedded in a starPEG-heparin hydrogel showed higher viability rate in comparison with the pseudoislets embedded in an alginate hydrogel, and naked pseudoislets.

- The computational simulation confirmed the oxygen deficiency in the islets of a bigger size and their tendency to form a hypoxic core even in the presence of an additional oxygen source.
- The PDMS-CaO_2 disks were shown to produce sufficient amounts of oxygen over a period of 28 days.

Conclusions: The advanced embedding matrix based on an ECM-mimicking hydrogel platform (starPEG-heparin hydrogel) shows a high potential in improving survival and functionality of an islet graft. Due to the sustained long-term oxygen release the presented customized oxygen generating module is expected to further improve islets survival as well in the early post-implantation period.

PP23

WITHDRAWN

PP24

PANCREATIC ISLET TRANSPLANTATION IN TYPE 1 DIABETES: 30-YEAR EXPERIENCE FROM A SINGLE-CENTRE COHORT IN ITALY

Davide Catarinella*[1], Stefano Tentori[2], Agnese Gobbi[1], Chiara Gremizzi[2], Rossana Caldara[2], Vera Paloschi[2], Paola Magistretti[2], Lorenzo Piemonti[1], Paola Maffi[1]

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Background: Pancreatic islet transplantation is an effective treatment to B-cell replacement for selected people affected by type 1 diabetes. It is a confirmed approach to stabilize frequent and unaware episodes of hypoglycemia, to prevent glycemic lability and to reduce insulin resistance induced by intensive care; however, data on long-term experience remain limited. We report outcomes from a single-centre cohort up to 30 years after islet transplantation.

Methods: In this cohort study we enrolled patients older than 18 years affected by type 1 diabetes who underwent allogenic pancreatic islet transplantation between 1989 and 2022 at San Raffaele Hospital in Milan, Italy. We included patients who underwent islet transplantation alone and patients who underwent islet after kidney transplantation. The data analyzed were the overall survival of patients, the graft survival (fasting C-peptide > 0.3 nmol/l), the period of insulin-independence, the glycemic control and the short and long-term adverse events. We performed a multivariate binary logistic regression to determine predictors of sustained graft survival.

Results: Between 1989 e 2022 we included 153 patients who underwent islet transplantation (88 islet transplantation alone). 81 patients were females (46 islet transplantation alone). Median follow-up was 4.7 years. Median graft survival was 45 months for transplantation after kidney transplant, 41 months for transplantation-islet alone. Early graft failure occurred in 5 patients of transplantation after kidney transplant and in 18 patients of transplantation-islet alone group. Patients in the islet transplantation alone-group remained insulin-independent for a mean period of 41 months, while patients in the group of islet after kidney transplant for 23 months. Patients with sustained graft survival had higher rates of insulin independence and sustained improvement in glycemic control compared with patients with non-sustained

graft survival. In patients with sustained graft survival the incidence of peri-procedural complication was lower.
Conclusions: We reported a single center cohort study of long term outcomes after islet transplantion. The limitation of this study was the retrospective approach, the small sample size and the absence of non-transplanted patients.

PP25

PROGNOSIS OF KIDNEY FUNCTION AFTER ISLET TRANSPLANTATION ALONE (ITA) IN TYPE 1 DIABETES (T1D) AT 10 YEARS (PRONOCELDIAB STUDY NCT02627690).

Robin Ellena[1], Mehdi Maanaoui[2], Frederique Defrance[1], Kristell Le Mapihan[1], Mikael Chetboun[3], Arnaud Jannin[1], Julie Kerr-Conte[4], Francois Pattou[3;4], Marie-Christine Vantyghem*[1;4]

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Background: Few studies have assessed the impact of islet transplantation on the long-term complications of T1D. The objective was to evaluate the nephrological complications of a cohort of T1D ten years after evaluation for an ITA, according to the realization or not of this islet transplantation.

Methods: Monocentric study conducted from 2014 to 2021 in a cohort of T1D patients having consulted for ITA, comparing the loss of estimated glomerular filtration rate (eGFR) over the 10 ± 2 years period following ITA, between the islet-transplanted group (according to the Edmonton protocol) and the control group treated with optimized insulin therapy (controls).

Results: 86 T1D constituted this cohort, of which

- 34/86 did not receive ITA but were not included in Pronoceldiab: 1) 13 initially, due to a contraindication to ITA (6 proteinuria, 3 residual C-peptide, 2 psychological disorders, 1 ischemic heart disease, 1 obesity; 2) 21 for lack of reassessment at 10 years (3 deaths, 3 kidney-pancreas transplants, 8 unreachable, 7 refusals).
- 16/86 T1D who did not receive ITA were included in Pronoceldiab (Controls)
- Of the 36 islet-transplanted patients, 17 with a follow-up of 10±2 years were included in PRONOCELDIAB (ITA group).

At T0, sex ratio, age, duration of diabetes, HbA1c, creatinine, eGFR and microalbuminuria did not differ between ITA and control groups. BMI was higher in controls. At 10±2 years, loss of eGFR, eGFR and microalbuminuria were similar between ITA and controls, unlike serum creatinine. Loss of eGFR in the ITA group was influenced favorably by the duration of insulin independence and unfavorably by age, overweight and initially poor renal function. Over the ten-year period, mortality seemed higher in controls (≥3/50 vs. ITA 0/36).

Conclusions: This study does not show any difference in eGFR deterioration at 10 years between the ITA and insulin therapy groups, despite treatment with anticalcineurins in islet-transplanted recipients.

PP26

RETROSPECTIVE ANALYSIS OF CGM AND FGM DATA OF PATIENTS AFTER PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION AND PATIENTS AFTER PANCREATECTOMY ALONE

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Background: Patients after total pancreatectomy have extremely labile form of diabetes, due to lack of insulin and glucagon, irregular carbohydrate absorption in the gastrointestinal tract, and impaired gastrointestinal hormones secretion. Autotransplantation of pancreatic islets o"ers a unique possibility to prevent this therapeutically challenging type of diabetes.
Methods: To assess the impact of autotransplantation on diabetes compensation we performed a retrospective analysis of the available data from continuous and flash glucose monitoring (covering 12 months) in a cohort of patients after autotransplantation (n=9) and patients after total pancreatectomy without autotransplantation treated in our centre (n=9).
Results: All of the patients after autotransplantation had detectable levels of C-peptide, 3 do not need insulin therapy, and others require small doses. They had significantly better diabetes compensation compared to the cohort without autotransplantation (glycated haemoglobin 50.4 ± 8 mmol/mol vs. 66.2 ±13 mmol/mol, p=0.036; average glucose levels 7.4 ± 1.4 mmol/l vs. 10.2 ± 2.1 mmol/l, p=0,004) and spent significantly more time in recommended range of glucose levels 3.9-10 mmol/l (average time in range 84 ± 15 % vs. 51.4 ± 19 % p= 0.0017), less time in hyperglycaemia and hypoglycaemia, with lower glycaemic variability (coe#cient of variation 25 ± 5 % vs. 37 ± 5 %, p=0.006) and required lower daily doses of insulin (0,25 ± 0,2 IU/kg vs 0,49 ± 0,2 IU/kg, p=0.02).
Conclusions: Islet autotransplantation can preserve endogenous insulin and glucagon secretion and enable more stable glucose control. Therefore it should be considered in all patients referred to pancreatectomy for benign causes.
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CLINICAL: PANCREAS

PP27

COVID-19 PANDEMIC DOES NOT AFFECT GRAFT AND PATIENT SURVIVAL IN HIGH VOLUME CENTER

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Background:Covid 19 pandemic had a strong impact on pancreatic transplantation activity. Initial reports suggested severe course in solid organ transplantation patients with mortality exceeding 20 %.. The number of transplants declined during Covid 19

pandemic worldwide. High Covid 19 related mortality among solid organ recipients and shortage of ICU beds decrease number of all transplanted organs but pancreas was the most affected -17% decrease. The aim of the study was to evaluate the safety and effectiveness of SPK (simulltaneous pancreatic kidney transplantation) during Covid 19 pandemic

Methods: The retrospective analysis of SPK performed in polish high volume Center in period from 2020 to 2022

Results: 21 SPK were performed on patients with diabetes type 1(11 woman, 10 man). In postoperative period one patient had pancreatic graftectomy due to severe graft pancreatitis . All others had well functioning both pancreatic and kidney allografts. They stayed free from insulin as well from dialysis therapy. The functional results using IGLS criteria were comparable to pre pandemic ones.

Conclusions: Despite previous concerns about safety of the pancreatic transplantation in Covid 19 pandemic SPK performed in experienced Center appeared to be safe procedure associated with positive outcome regarding both grafts and patient survival

PP28

DIABETES-ASSOCIATED HLA DONOR GENOTYPES AND PANCREAS TRANSPLANT OUTCOMES

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Background: The genotypes HLA DR3/DR4, DR3/DR3, DR4/DR4 are associated with a predisposition to diabetes. Two previous studies have considered whether pancreas transplant outcomes are worse in donors expressing these HLA genotypes. This study evaluated UK recipient outcomes after pancreas transplantation from donors with a diabetes-associated genotypes.

Methods: Data on all UK pancreas transplants from 2004-2019 was obtained from the NHSBT-UK Registry, n=2,938. HLA-DR type was recorded for all organ donors. Re-transplants and those missing patient or graft survival were excluded, resulting in a final cohort of n=2,661. Univariate analyses were conducted using Kaplan-Meier plots and multi-variate analysis using Cox-regression models. Complications were analysed using chi-squared analyses.

Results: The majority of grafts were from donors not associated with diabetes genotypes (90.1%, n=2397) whereas 5.4% (n=145) came from HLA DR3/DR4 donors, 1.6% (n=43) from DR3/DR3 and (n=76) 2.9% from DR4/DR4. Donors were well matched in terms of characteristics. Univariate analysis showed comparable outcomes in graft (GS) and patient (PS) survival between donor-HLA-genotypes at 1year (GS *p=0.504*; PS *p=0.817*) and 3years (GS *p=0.641*; PS *p=0.943*;). We further delineated our categories into SPK, PTA and PAK as a previous study suggested different recipient categories may be adversely affected. Again, we saw comparable outcomes in GS at 1 yr (SPK p=0.980, PTA p=0.759, PAK p=0.244) and 3 yrs (SPK p=0.708, PTA p=0.744, PAK p=0.275) and PS at 1y r (SPK p=0.553, PTA p=0.527, PAK p=0.756) and 3 yrs (SPK p=0.728, PTA p=0.928, PAK p=0.424). Multivariate analysis also failed to reveal a statistically significant difference between GS (p=0.604, HR

1.041, 95%CI 0.895, 1.211) or PS (p=0.623, HR 1.045, 95%CI 0.876, 1.248). There were also no differences in complication rates.
Conclusions: This multicentre UK study has found comparable survival outcomes and complication rates within our donor-HLA-genotype groups. We do not believe that the presence or absence of a diabetes-associated HLA-genotype bears any influence on outcomes for either SPK or solitary pancreas transplants.

PP29

EARLY-PHASE CLINICAL TRIALS OF BIO-ARTIFICIAL ORGAN TECHNOLOGY: A SYSTEMATIC REVIEW OF ETHICAL ISSUES

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Background: Regenerative medicine has emerged as a potential response to the persistent problem of shortage of donor organs in the field of organ transplantation. The VANGUARD project aims to develop bioartificial pancreases for transplantation into non-immunosuppressed diabetic type 1 patients. Similarly, in other disease areas, transplantable bio-artificial organs are being developed. Eventually researchers will reach a point to suggest that bio-artificial organs might be beneficial and safe for humans. In early-phase clinical trials, research participants could be exposed to serious risks. As of yet, there is no ethical guidance for the conduct of early-phase transplantation trials of bio-artificial organs.
Methods: We systematically reviewed the literature in adjacent fields of research (e.g. cell-based therapy, 3D bioprinting and tissue-engineering) and examined relevant ethical points to consider for early-phase clinical trials of transplantable bioartificial organs.
Results: 92 articles on ethics of early-phase clinical trials in adjacent fields were included. Six themes were identified: cell sources, risk-benefit assessment, patient selection, trial design, informed consent, and oversight and accountability.
Conclusions: The results will be valuable for researchers and clinicians with an interest in regenerative medicine and involved in the translation of bio-artificial organs for clinical transplantation. Further empirical research is needed to provide insight in patient perspectives.

PP30

HYPERTENSION IN THE DONOR IS ASSOCIATED WITH AN INCREASED RISK OF EARLY PANCREAS ALLOGRAFT FAILURE

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Background: About 10-20% of pancreas allografts are still lost in the very early postoperative period despite the identification of numerous risk factors that correlate with graft thrombosis.
Methods: We conducted a multicenter study including 899 pancreas transplant recipients between 2000 and 2018. Early pancreas failure occurring before the 30th postoperative day, long-term pancreas survival, kidney survival and patient survival were analyzed and adjusted to several donor, recipient and perioperative transplantation variables using a multivariate cause-specific Cox model also stratified to transplant centers.
Results: Pancreas from donors with hypertension, as well as with high body mass index, were independently associated with an increased risk of early pancreas failure (respectively, HR= 2.43, 95% CI from 1.32 to 4.49 and HR= 1.38, 95% CI from 1.13 to 1.68). Donor hypertension also impacted long-term pancreas survival (HR= 1.88, 95% CI from 1.13 to 3.12). However, when pancreas survival was calculated after the postoperative day 30, donor hypertension was no longer a significant risk factor (HR= 1.22, 95% CI from 0.47 to 3.15).
Conclusions: Donor hypertension was a significant independent risk factor of early pancreas failure. Unknown mechanisms linked to hypertension are possibly involved and will need further studies to allow effective preventive interventions.

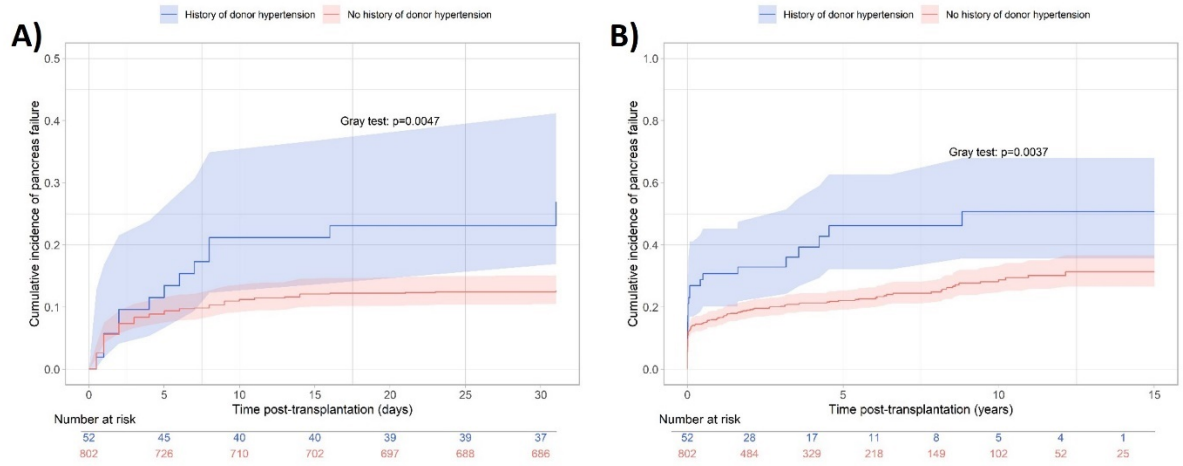

Figure. **A.** Cumulative incidence of pancreas failure within the first 30 days after transplantation according to history of donor hypertension (Aalen-Johansen estimator). **B.** Cumulative incidence of pancreas failure in the long-term according to history of donor hypertension (Aalen-Johansen estimator).

Table. Multivariable cause-specific Cox model associated with the risk of pancreas graft failure within the first 30 days post-transplantation (n= 786, 113 observations removed because of missing data).

	HR	**95% CI**	**p-value**
Pancreas cold ischemia time (hours)	1.05	[0.98 ; 1.14]	0.1814

	HR	95% CI	p-value
Donor age (years)	1.00	[0.98 ; 1.02]	0.7855
Donor BMI (kg/m²)	1.11	[1.04 ; 1.19]	0.0017
Donor history of hypertension	2.43	[1.32 ; 4.49]	0.0044

BMI, body mass index; CI, confidence interval; HR, hazard ratio. The model was stratified on the center.

PP31

WITHDRAWN

PP32

LONG-TERM IMPACT OF COVID-19 ON PANCREAS AND ISLET TRANSPLANTATION IN THE UK

Claire Counter*[1], John Casey[2], James Shaw[3], Simon Harper[4], Sanjay Sinha[5], Chris Callaghan[6;7], Martin Drage[6], Paul Johnson[8], Doruk Elker[9], Anand Muthusamy[10], Andrew Sutherland[2], David Van Dellen[11], Colin Wilson[12], Derek Manas[7;12], Steven White[12]

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Background: The World Health Organization declared a pandemic of coronavirus disease SARS-CoV-2 (COVID-19) on 11 March 2020. In this analysis, the long-term impact of COVID-19 on beta cell replacement therapy in the UK was reviewed.

Methods: Pancreas and islet donation and transplant activity during the period 11 March 2020 to 10 March 2021 (COVID year) was compared with the same period in the previous (pre-COVID) and following (post-COVID) years. One year graft survival was compared using the Kaplan-Meier method. The outcome of patients on the transplant waiting list at 1 February 2020 and the current waiting list were analysed.

Results : In the COVID year, 97 whole pancreas and islet (81 simultaneous pancreas and kidney (SPK), 3 solitary pancreas, 5 simultaneous islet and kidney, 8 solitary islet) transplants were performed in the UK, a reduction of 54% compared with 212 in the

pre-COVID year. In the post-COVID year, 154 transplants were performed: 59% higher than the COVID year but still 27% lower than the pre-COVID year. The proportion of transplants including a kidney was 84% in the COVID year compared with 79% and 77% for pre- and post-COVID years, respectively. 40 islet isolations were performed in the COVID year, with 33% resulting in transplant compared with 31% and 38% in the pre- and post-COVID years, respectively. One year pancreas graft survival following SPK transplant was 96%, 95% and 95% for pre-COVID, COVID and post-COVID time periods respectively, p=0.8. Of the 12 islet transplants with follow-up, 2 had failed within a year. 238 patients were active on the transplant list on 29 February 2020. By 10th October 2022**:** 147 had been transplanted; 14 had died; 27 had been removed and 50 remained active or suspended on the list. The total number of patients active or suspended on the pancreas or islet transplant list at the end of February was 467 in 2020, increasing by 20% to 562 in 2022. For 238 whole pancreas patients active on the list at end of February 2020, the median waiting time (interquartile range) was 218 days (86-425) and for 276 patients in 2022 was 255 days (136-463).
Conclusions: In the UK, pancreas and islet transplantation activity has not fully recovered to pre-COVID levels and the transplant waiting list has increased by 20% over 2 years. One year pancreas graft survival is similar for all three time periods.

PP33

LONG-TERM OUTCOMES OF BETA CELL REPLACEMENT IN PEOPLE LIVING WITH HIV (PLWH), TYPE I DIABETES (T1DM), AND RENAL FAILURE

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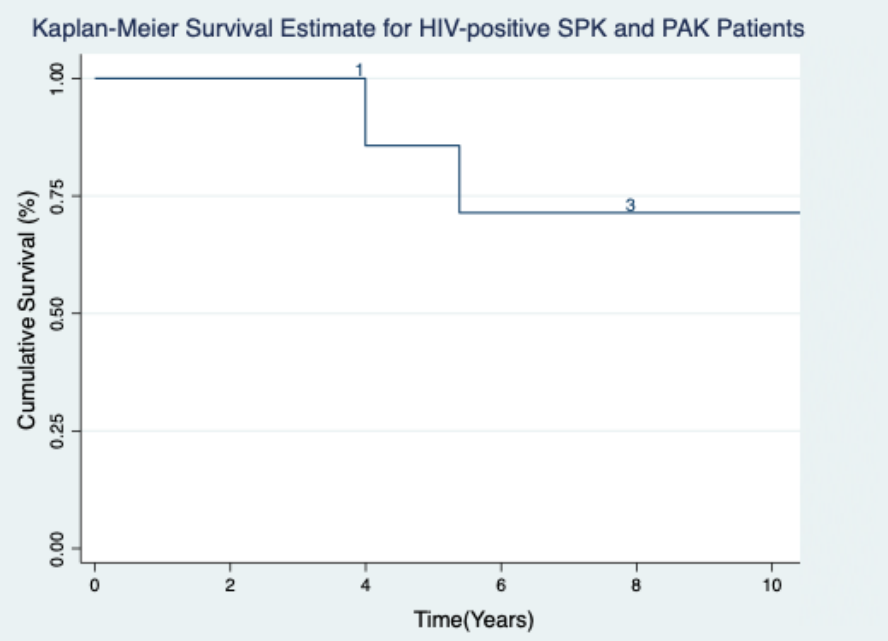
Background: Transplantation in PLWH has required a careful balance of immune system modulation to avoid rejection and infection in a group of recipients that are theoretically immunocompromised as a result of chronic HIV infection. We present the long-term results of 10 HIV-positive patients with T1DM and renal failure who underwent beta cell replacement therapy.
Methods: This is a single-center retrospective cohort study of 10 consecutive patients with T1DM and renal failure who underwent beta cell replacement therapy between May 2006 and January 2019. Seven patients underwent simultaneous pancreas kidney (SPK) transplants and 1 patient underwent a pancreas after kidney (PAK) transplant. Two patients were excluded from solid organ transplant due to cardiovascular risk factors and instead underwent islet after kidney (IAK) transplant. All solid organ pancreas patients received Thymoglobulin for induction and remained on lifelong steroids following their transplants.
Results: Mean follow-up time for all solid organ pancreas transplant recipients (n = 8) was 7.0 years (range 3.8 to 11.2 years) and pancreas and kidney graft loss occurred in 1 patient. Mean Hemoglobin A1C was 5.5% (range 4 – 7.6) at last follow-up. There were 3 deaths secondary to cardiovascular events and 7/8 patients remained insulin independent at the time of death or last follow-up. Pancreas rejection occurred in 2/8 patients and was successfully reversed in 1/2 patients. BK viremia developed in 4/8 patients, which occurred following treatment for rejection in 2/4 patients. Both IAK

recipients became insulin independent with one recipient remaining insulin independent at the time of death. Both IAK recipients died of cardiovascular events.
Conclusions: Long-term follow-up data from a cohort of PLWH who underwent beta cell replacement therapy for T1DM and renal failure demonstrate low rates of rejection, graft loss, and infectious complications, with the exception of BK viremia. PLWH are excellent candidates for beta cell replacement strategies contingent upon the cardiovascular comorbidities associated with chronic HIV.

Table 1: Hemoglobin A1C values at 1, 3, 5, and 10 years following beta cell replacement therapy

	HbA1C at 1 year	HbA1C at 3 years	HbA1C at 5 years	HbA1C at 10 years
Patient #1 (SPK)	5.1	4.6		
Patient #2 (SPK)	5.2	5.6	5.3	6.5
Patient #3 (SPK)	5.2	5.6	5.5	5.9
Patient #4 (SPK)	5.7	6.7		
Patient #5 (PAK)	5.5	5.7	5.6	5.7
Patient #6 (SPK)	3.5	3.5	4.3	
Patient #7 (SPK)	5.4	3.9	6.2	
Patient #8 (SPK)	4.2	4		
Mean HbA1C after SPK or PAK	**5.0**	**5.0**	**5.4**	**6.0**
Patient #9 (IAK)	4.9	5.4		
Patient #10 (IAK)	7.1	6.8	7.6	
Mean HbA1C after IAK	**6.0**	**6.1**	**7.6**	

Figure 1: Kaplan-Meier Patient Survival for HIV-positive SPK and PAK Recipients



PP34

LONGTERM RESULTS COMPARING LIFECYCLE PHARMA TACROLIMUS TO HIGH DOSE STANDARD TACROLIMUS IN FAST METABOLIZING PANCREAS RECIPIENTS: A CENTER EXPERIENCE

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Background: We retrospectively analyzed the long-term clinical outcome in Tacrolimus (TAC) fast-metabolizing pancreas recipients by comparing one group with LifeCycle Pharma Tacrolimus (LCPT) to the control group with high dose extended release TAC (ER-TAC).

Methods: Between 2016 -2019 totally 30 TAC fast-metabolizing (definition: TAC concentration/dosage = c/d ratio <1.05) type 1 diabetics underwent pancreas transplantation at our center, among them 28 combined with kidney transplantation. Fifteen patients were converted to LCPT (group 1) and fifteen received high dose ER-TAC (group 2). The aimed TAC trough-level (ng/mL) was 12-14 in the first month, 6-8 at month 12 and 5-7 thereafter. The immunosuppressive regimen consisted of a lymphocyte depleting induction agent, MMF, steroids. The surgical procedure was performed according to standard techniques. We retrospectively analyzed pancreatic and renal graft survival and function, significant complications, TAC dosage and levels, lymphocyte account at mean observation period of 48.2 (36-63) months.

Results: One patient in group 1 died at month 37 due to SARS CoV pneumonia, resulting in a patient survival of 93.3 %. The patient survival in group 2 was 100%. The pancreas / renal graft survival in group 1 was 100% / 100% respectively, and 86.7 % / 93.3 % in group 2: both pancreatic grafts were lost for thrombosis (month 2, 13), the kidney for chronic humoral rejection (month 48). Apart from the fatal SARS CoV pneumonia all significant complications in both groups were controllable. One patient in group 1 gave birth to a healthy son at month 32. The TAC formulations in both groups were kept in the longterm period apart from one patient in group 1 who converted herself to ER-TAC at month 2 for diarrhoea without improvement, obviously basing on a psychosomatic disorder.

The pancreatic and renal function in the surviving grafts at month 48 were comparable in group 1 / group 2 with mean values of HbA1c (g%) 5.4 / 5.4, serum creatinine (mg/dL) 1.3 / 1.2, absolute lymphocyte account (G/L) 1.76 / 2.0, TAC-level (ng/mL) 6.3 / 7.0, dosage of LCPT / ER-TAC (mg/kg) 0.052 / 0.06 and c/d ratio 1.99 / 2.07, respectively.

Conclusions: We conclude from our data that LCPT and ER-TAC in TAC-fast - metabolizing pancreas recipient outcomes are comparable in the long term. Further studies are of interest.

PP35

CAPSULE-BASED REFILLING STRATEGY FOR AN IMPLANTABLE INSULIN DELIVERY DEVICE OPTIMIZED ON HUMAN ANATOMY MODEL

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Salamone[1], Veronica Iacovacci[2], Arianna Menciassi[2], Leonardo Ricotti[2], Fabio Vistoli[1]
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Background: Intraperitoneal insulin delivery using implantable pumps is a promising solution for glycemic control in type-1 diabetes. It results in fast insulin pharmaco-kinetics and pharmaco-dynamics that well mimic human physiological delivery. In the solutions currently available on the market, the refilling procedure is invasive and brings with it complications and discomfort.
Methods: This study aims to optimize the design of a refilling strategy through ingestible capsules for an implantable insulin delivery system, tailored on human anatomy. We devised a new layout to guarantee a stable and reliable capsule capture. It includes two independent magnetic docking units, based on magnetic switchable circuits, which are sequentially activated to dock a capsule. Finite element simulations were used to assess the docking force exerted on the capsule for different magnet dimensions and capsule-device distances. Bench tests were performed to validate the simulation results and measure the force that the magnetic system has to overcome for guaranteeing stable docking.
Results: The optimized system was included in a mock-up of the device (kidney-shaped, 55 x 30 x 65 mm^3) and implanted in an intraperitoneal pouch of two human cadavers (male and female). After the implantation, the attraction force and the capsule-device distance were measured both in- and ex-situ. Results showed that the magnetic force obtained in the in-situ (3.13 ± 1.84 N) and ex-situ (2.78 ± 0.32 N) tests were in good accordance with the simulation results.
Conclusions: The system validation on human cadavers confirmed the suitability of the implantation procedure and allowed to identify other important parameters for further development of this technology.

PP36

PREDICTING FUNCTION DELAY WITH A MACHINE LEARNING MODEL: IMPROVE THE LONG-TERM SURVIVAL OF PANCREATIC GRAFTS

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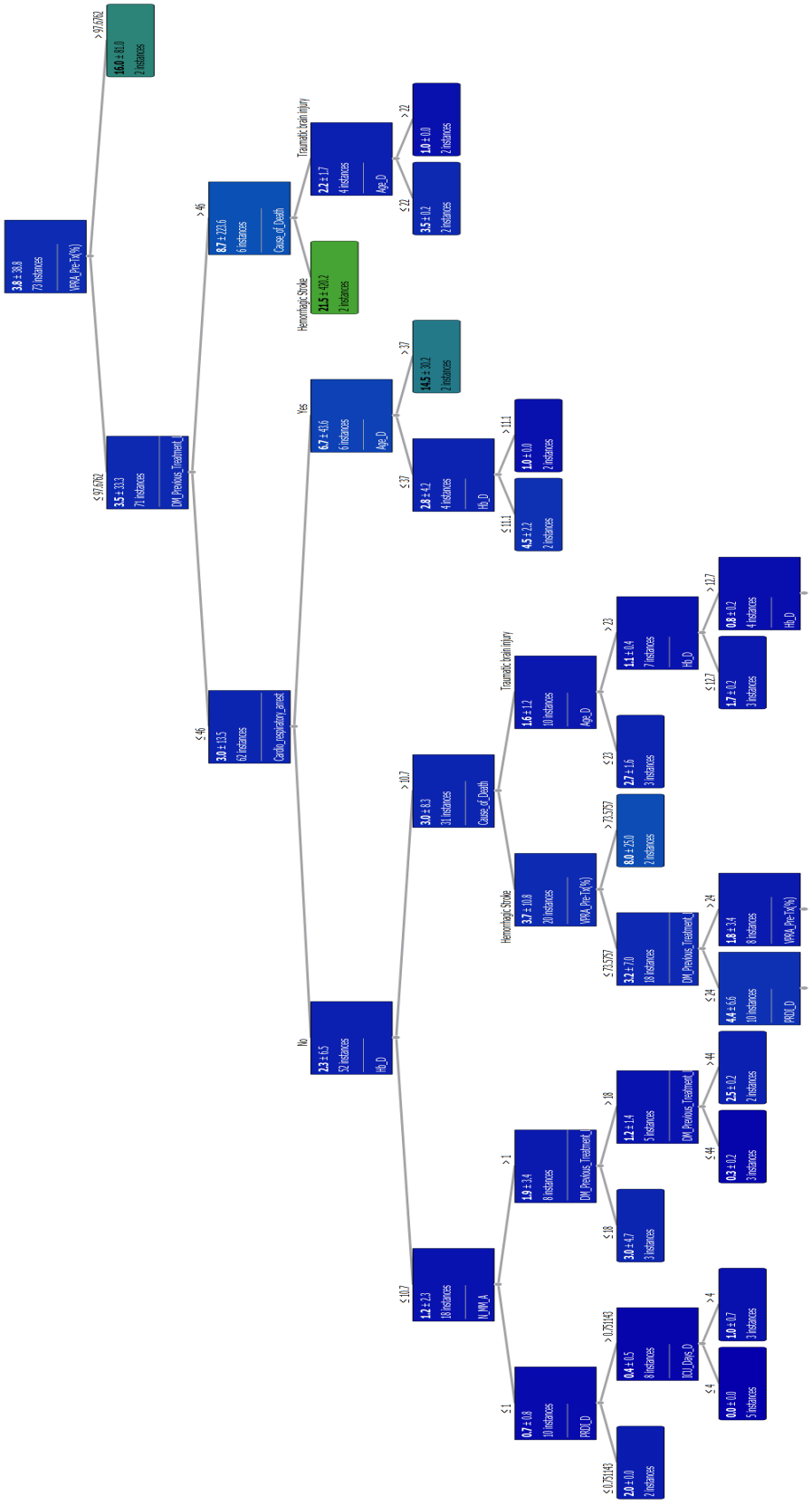
Background: The impact of delayed graft function on outcomes following various solid organ transplants is well documented and addressed in the literature. Delayed graft function following various solid organ transplants is associated with both short- and long-term graft survival issues.

Methods: We performed a single-center retrospective cohort study between March 2011 and January 2020 including 106 patients and evaluated whether pancreas graft survival differs according to moment of insulin therapy following simultaneous pancreas-kidney transplant. There were 42 overall features considered, 12 categorized and 30 numerical, grouped into three categories: Recipient, donor, and peri-operative. Kaplan-Meier estimator was used to examine post-transplant patient, graft, and death-censored graft survival (IBM SPSS Statistics v.28.0). All experiments in this work were carried out with the Orange data mining open-source machine learning software.
Results: As a result, we aimed to identify possible risk factors and build a machine-learning-based model that predicts the likelihood of dysfunction following SPK transplant patients based on day zero data after transplant, allowing to enhance pancreatic graft survival. Feature selection by Relief algorithm yielded donor features, age, cause of death, hemoglobin, gender, ventilation days, days in ICU, length of cardiac respiratory arrest and recipient features, gender, long-term insulin, dialysis type, time of diabetes mellitus, vPRA pre-Tx, number of HLA-A mismatches and PRDI, all contributed to the models' strength.
Conclusions: So, with the use of versatile and practicable machine learning models it is possible to identify patients at risk of decreased graft survival in order to improve clinical decision-making and adjust the protocols of exogenous insulin administration as well as immunosuppression in the immediate post-transplant period.

Model	**Definition of pancreas endocrine DGF**	**% of patients with DGF (n)**	**Feature selection (Top Scoring method)**	**Features included (n) Description**	**Top Models (AUC-ROC/CA)**
1	Need for scheduled exogenous insulin at the time of discharge from hospital after a technically successful SKP transplant	19% (14)	Information Gain	(12) Pregnancy Female (R)* Cause of Death (D)* Hb (D) Creatinine (D) DM Previous Treatment Long Term Insulin U/l/day (R) BMI (R)* Weight (R)* HbA1c Pre-Tx (R) ICU Days (D) ASA (R)* Urea (D) vPRA Pre-Tx(%) (R)	1-Neural Network 0.89/0.86 2-SVM 0.85/0.85 3-Logistic Regression 0.84/0.84
2	No need for scheduled exogenous insulin after a technically successful SKP transplant	84% (62)	Chi-square	(13) Height (R), PRA CDC max (>10%) (R), Hb (D)* N MM HLA-A (R), Age (D), Pre Transplant Flow Crossmatch (R), Height (D), BMI (D), Cardio respiratory arrest (D), ICU Days (D), ASA (R), Cause of Death (D), Dialysis time (days) (R)	1-AdaBoost 0.77/0.86 2-Tree 0.71/0.85 3- Naïve Bayes 0.69/0.67
3	Need for scheduled exogenous insulin at least 1 day after a technically successful SKP transplant	56% (41)	Chi-square	(9) BMI (R)* HbA1c Pre-Tx (R) PRA CDC max (>10%) (R) vPRA Pre-Tx (%) (R) Cause of Death (D) Height (R) N MM HLA-DR (R)* PRDI (D) BMI (D)	kNN 0.67/0.63
4	Need for scheduled exogenous insulin at least 2 days after a technically successful SKP transplant	41% (30)	Information gain ratio	(13) Arterial Reconstruction (S) Pre Transplant Flow Crossmatch (R) Number of transfusions (ECU) (R) Pregnancy Female (R) N MM HLA-DR (R)* DM time (days) (R) N MM HLA-B (R) Type of Dialysis (R)* Blood Transfusion Intra-op (S) Warm Ischemia (m) (S) Previous Tx (R) Cause of Death (D) Total Operating Time (m) (S)	1-Naïve Bayes 0.85/0.81
5	Need for scheduled exogenous insulin at least 3 days after a technically successful SKP transplant	27% (20)	Gini coefficient	(12) Urea (D) Blood Transfusion Intra-op (S) N MM HLA-DR (R)* Dialysis time (days) (R) BMI (R)* Number of transfusions (ECU) (R) Cause of Death (D) DM time (days) (R) Total Operating Time (m) (S) Creatinine Pre-Tx (R) Type of Dialysis (R) Warm Ischemia (m) (S)	1-Naïve Bayes 0.85/0.79
6	Need for scheduled exogenous insulin at least 4 days after a technically successful SKP transplant	19% (14)	FCBF (Fast Correlation Based Filter)	(10) Blood Transfusion Intra-op (S) Pre Transplant Flow Crossmatch (R) BMI (R)* Type of Dialysis (R) Cardio respiratory arrest (D) Arterial Reconstruction (S) Creatinine Pre-Tx (R)* DM time (days) (R) Cause of Death (D) Total Operating Time (m) (S)	1-Naïve Bayes 0.88/0.82
7	**Stop&Start**	15% (11)	Gini coefficient	(7) Pregnancy Female (R)* Cause of Death (D)* HbA1c Pre-Tx (R)* Urea (D) DM Previous Treatment Long Term Insulin U/l/day (R)	1-Naïve Bayes 0.93/0.89


3.8 ± 30.8
73 instances
VIRAL_Pre-Tx(%)
> 97.6762
16.0 ± 96.0
2 instances
≤ 97.6762
3.5 ± 23.3
71 instances
DM_Previous_Treatment_I...
> 46
8.7 ± 223.6
6 instances
Cause_of_Death
Traumatic brain injury
2.2 ± 1.7
4 instances
Age_D
> 22
1.0 ± 0.0
2 instances
≤ 22
3.5 ± 0.2
2 instances
Hemorrhagic Shoke
21.5 ± 450.2
2 instances
≤ 46
3.0 ± 13.5
62 instances
Cardio_respiration_arrest
Yes
6.7 ± 45.6
6 instances
Age_D
> 37
14.5 ± 361.2
2 instances
≤ 37
2.8 ± 4.2
4 instances
Hb_D
> 11.1
1.0 ± 0.0
2 instances
≤ 11.1
4.5 ± 2.2
2 instances
No
2.3 ± 6.5
52 instances
Hb_D
> 10.7
3.0 ± 8.3
31 instances
Cause_of_Death
Traumatic brain injury
1.6 ± 1.2
10 instances
Age_D
> 23
1.1 ± 0.4
7 instances
Hb_D
> 12.7
0.8 ± 0.2
4 instances
Hb_D
≤ 12.7
1.7 ± 0.2
3 instances
≤ 23
2.7 ± 1.6
3 instances
Hemorrhagic Shoke
3.2 ± 10.8
20 instances
VIRAL_Pre-Tx(%)
> 73.7797
8.0 ± 25.0
2 instances
≤ 73.7797
3.2 ± 7.0
16 instances
DM_Previous_Treatment_I...
> 24
1.8 ± 3.4
8 instances
VIRAL_Pre-Tx(%)
≤ 24
4.4 ± 6.6
10 instances
PROD_D
≤ 10.7
1.2 ± 2.3
16 instances
N_MVI_A
> 1
1.9 ± 3.4
8 instances
DM_Previous_Treatment_I...
> 18
1.2 ± 1.4
5 instances
DM_Previous_Treatment_I...
> 44
2.5 ± 0.2
2 instances
≤ 44
0.3 ± 0.2
3 instances
≤ 18
3.0 ± 4.7
3 instances
≤ 1
0.7 ± 0.8
10 instances
PROD_D
> 0.7751143
0.4 ± 1.5
8 instances
IDU_Days_D
> 4
1.0 ± 0.7
3 instances
≤ 4
0.0 ± 0.0
5 instances
≤ 0.7751143
2.0 ± 0.0
2 instances

PP37

RECIPIENT OUTCOMES AFTER SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANT DELINEATED BY DONOR CRCL

Ruth Owen*[1], Niall Fitzpatrick[2], Claire Counter[3], Abdullah Malik[1], Balaji Mahendran[1], Samuel Tingle[1], Derek Manas[1;3], Neil Sheerin[1;4], Colin Wilson[1;4], Steve White[1;4]

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Background: Increasing demand for simultaneous pancreas and kidney transplantation (SPK) has led to extension of the donor criteria for transplantation . The use of grafts from donors with a lower than normal Creatinine Clearance (CrCl) has not been fully investigated after SPK. The study aimed to assess if using these kidneys had any adverse effect on patient and graft survival.

Methods: Data on all UK SPKT's from 2001-2021 were obtained from the NHSBT UK Transplant Registry (n=2,631). Data was available on terminal serum creatinine only enabling delineation of different CrCl of donor kidneys. It was not possible to delineate whether the terminal CrCl was due to an acute kidney injury (AKI). Cases with no information pertaining to CrCl or where the recipient received a re-transplant were removed, leaving a final cohort of 1,819 (69.1%). CrCl was calculated using the Cockroft-Gualt equation. Pancreas Graft (PGS), Kidney Graft (KGS) and patient survival analyses were conducted using Kaplan-Meier plots and Cox-regression models.

Results: The majority of SPKT grafts were from donors with an CrCl>90 (73%, n=1,327), and 27% (n=492) were from donors with an CrCl<90. Donors with an CrCl <90 were statistically significantly more likely to be female (p<0.0001), a DBD donor (p=0.014) and have a lower BMI (p<0.0001). Recipients who received a graft from a donor with an CrCl<90 were more likely to be from a BAME community (p=0.027). Univariate analysis showed a statistically significant decreased PGS (p=0.023) and KGS (p=0.005) when the donor had an CrCl<90. This trend was not seen when comparing patient survival. Multi-variate analysis also showed comparable outcomes in PGS (p=0.311, HR 1.127, 95%CI 0.894, 1.422) and PS (p=0.312, HR 0.866, 95%CI 0.656, 1.144) but poorer outcomes for KGS (p=0.021, HR 1.351, 95%CI 1.046,1.746).

Conclusions: This is the largest reported study evaluating outcomes after SPKT delineated by a terminal donor CrCl. We accept a lower CrCl could be indicative of either an AKI or an element of chronic kidney disease. In this current data analysis we have been unable to successfully distinguish between the two however we have shown poorer KGS in those with a lower CrCl (<90) but not at the expense of pancreas graft survival or patient survival. Further analysis is needed to explain the precise reasons for the lower CrCl's.

PP38

SERUM MARKERS OF EARLY GRAFT INJURY IN SIMULTANEOUS PANCREAS KIDNEY TRANSPLANT

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Background: Simultaneous pancreas kidney (SPK) transplants are life changing operations that can significantly improve patients' lives, reversing the metabolic abnormalities and other sequelae of diabetes. SPK transplants are not an insignificant operation however, placing recipients under considerable physiological stress. In the era of enhanced post operative recovery pathways, there are still no predictive biomarkers of hospital stay for SPK recipients.
Methods: We performed a single-centre retrospective cohort study of SPK recipients to assess whether serum markers of early graft injury could predict length of hospital stay. We used multiple linear regression models and log-transformed skewed continuous variables.
Results: 52 SPK recipients were included. When adjusting for donor age, recipient age and cold ischaemic time, CRP on post-operative day 2 and 3 significantly predicted length of hospital stay (Beta=0.396, P=0.004 and Beta=0.425, P=0.003 respectively). Patients with a day 2 CRP lower/higher than 68 had median stays of 23.3 vs 27.7 days. Patients with a day 3 CRP lower/higher than 89 had median stays of 23.5 vs 27.8 days. CRP on post-operative day 1, and amylase on post-operative days 1-3, did not predict hospital stay in crude or adjusted models.
Conclusions: CRP values on post-operative day 2 and 3 best predicted the length of hospital stay for SPK recipients. Day 1 CRP and amylase did not predict the length of hospital stay. This likely reflects the fact that CRP is a ubiquitous inflammatory marker, thereby having minimal value in the immediate post-operative phase. Manipulation of the pancreas graft during the procedure can also potentiate the release of amylase, rather than being a pure marker of graft injury post procedure. It may be possible to identify a cohort of patients who would benefit from a structured enhanced post operative recovery program to facilitate appropriate early discharge.

Characteristic	*N(%)*
Recipient gender	
Male	34 (65.4)
Female	18 (34.6)
Recipient age	
<40	22 (42.3)
40-55	24 (46.2)
>55	6 (11.5)
Donor age	
<20	10 (19.2)
20-30	9 (17.3)
30-40	9 (17.3)
40-50	20 (38.5)
>50	64 (7.7)
Type of graft	
DBD	31 (61.5)

DCD	3 (5.8)
Missing	17 (32.7)
Cold ischaemic time (pancreas)	Median 649 min (IQR 263min)

Table 1. Basic demographics

PP39

SIMULTANEOUS PANCREAS AND KIDNEY REPERFUSION IN IPSILATERAL SPK

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Background: Ipsilateral simultaneous pancreas-kidney transplantation(iSPK) is an attractive surgical strategy searching to reduce operative time and preserve the left iliac fossa for an eventual future transplant. Traditionally, pancreas is placed and reperfused first followed by kidney transplant. The aim of the study was to analyze a technical variant of iSPK.
Methods: A retrospective analysis was performed of 33 iSPK with simultaneous pancreas and kidney reperfusion from 2019 to 2021. Briefly, a wider cranio-caudal dissection of right iliac fossa was performed intended to fit both pancreas(more cranial) and kidney grafts. All the vascular anastomosis(pancreas vein and artery, kidney vein and artery) were performed first and next pancreas reperfusion was released, followed by a short hemostasis. After a few minutes kidney was also reperfused. Sequentially, exocrine drainage and uretheral anastomosis were performed. All PT were systemic(cava)-enteric drained, either by duodenal drainage or duodenojejunostomy.
Results: Donor and recipient age was 28.3(18-42) and 35.8(23-51) years and cause of donor death was cerebrovascular in 39% of cases. Mean surgical time was 322 min(235-420 min), pancreas and kidney cold ischemia time was, respectively, 519min(410-765min) and 526min(415-771min) and time interval between kidney and pancreas reperfusion was 7.3 min(1-65min). Blood transfusion was required in 4(12.1%) and kidney DGF occurred in 16(48.4%) patients. 1-year actuarial patient, kidney and pancreas graft survival was respectively 88%, 82% and 85% ,mean hospital stay was 8.0 days(4-30) and reoperations occurred in 7(21%) patients.
Conclusions: iSPK with simultaneous pancreas and kidney reperfusion is a variant technique of traditional iSPK that potentially shortens operative time, kidney cold ischemia time and also can minimize the time interval between pancreas and kidney reperfusion to only a few minutes. This initial series showed outcomes at least as good as other SPK techniques.

PP40

SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION HAD BECOME ALMOST EXCLUSIVELY METHOD -SINGLE CENTRE EXPERIENCE

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Background: SPK is recognized as a gold standard in diabetes type 1 treatment, but other types of pancreatic transplantation: PTA (pancreas transplant alone),PAK(pancreas after kidney) are recommended for patients with well functioning kidney .We recently observed the transition to almost exclusively performed SPK in our Centre. The aim of the study was to compare 5 years patients and pancreatic graft survival between SPK and solitary graft. .We put forward the hypothesis that other factors apart from Covid 19. pandemic may play a role.
Methods: This retrospective study concerned 245 patients who had undergone pancreatic transplantation in the period from 2005 to 2022.SPK-210 patients (86%), PTA 33 (13%),PAK 2 (1%).Patients and graft survival rate was observed
Results: 5 year patients and pancreatic graft survival were as follows SPK-86%/82 death censored rate, vs PTA 98%/45%. None of the PTA procedure was performed during the last four years
Conclusions: SPK had become prevailed procedure for pancreas transplantation despite excellent rate of patients survival after solitary transplant. This transition may be related to more advanced pharmacological treatment and better attainability of the last generation of continuous glucose monitors (CGM) and automated insulin delivery systems.

PP42

OUTCOMES OF SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANT - THE INFLUENCE OF DONOR AGE

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Background: Simultaneous pancreas-kidney transplantation (SPKT) is the treatment of choice for type 1 diabetic patients with end-stage renal disease, that restore long-term glycemic control. The impact of donor characteristics in long-term outcomes in SPKT is uncertain. We aimed to study the effect of donor age in graft and patient's survival in SPKT.
Methods: We retrospectively studied 254 patients submitted to SPKT between 2000 and 2021. Patients were classified as younger donor (donor age <40 years) and older donor (donor age >40 years). Kaplan-Meyer curves were performed to assess long-term graft and patient' s survival and groups compared by log-rank test.
Results: Fifty-three patients (21%) received grafts from older donors. Older donor group mean age was 44 ± 3years versus 25 ± 8years for the younger group. Recipient characteristics were similar between groups, except for body mass index which was lower in the older group (22,5 versus 21,7Kg/m2). Pancreas graft survival rates at 1, 5, 10 and 15 years were 89%, 83%, 77%, and 73% in the younger and 77%, 73%, 67% and 62% in the older donor group (p 0,052). Older donor [HR 1.88 95% CI:(1.11-3.20), p 0,020] and previous cardiovascular major events (MACE) [HR1.82 95%CI:(1.11-3.19), p 0,037] were associated with pancreas graft failure at 15 years. Kidney transplant survival (1, 5, 10 and 15 years) was significantly lower in the older donor cohort (94%, 92%, 69%, 60% versus 97%, 94%, 89%, 84% among younger donor; p=0,004). Older donor [HR2.70 95%CI:(1.36-5,39), p=0,005)], recipient' s age [HR0,92

95%CI:(0,87-0,98),p 0,008)] and previous MACE [HR2.05 95%CI:(1,01-4,16),p=0,005)] were predictive of kidney graft failure at 15 years. Patient survival rates at 1, 5, 10 and 15 years were 98%, 95%, 91%, and 81% in the younger versus 92%, 90%, 84%, and 72% in the older group (p=0,127).
Conclusions: Donor age seems to significantly influence long-term outcomes following SPKT. Older donor age was an independent predictor of both pancreas and kidney graft failure at 15 years. Pancreas graft and, particularly, kidney graft survival were significantly lower in the older donor group. Patient survival did not differ significantly between groups.

PP43

PANCREAS TRANSPLANTATION FROM SARS-COV-2 POSITIVE DECEASED DONORS

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Background: The use of pancreases from SARS-CoV-2 positive donors is of particular interest given the high levels of gut expression of the SARS-CoV-2 cellular entry angiotensin-converting enzyme 2 receptor, the duodenal tropism of SARS-CoV-2, and that SARS-CoV-2 can infect both exocrine and endocrine pancreatic tissues. Although non-lung organ transplantation from deceased donors with positive SARS-CoV-2 tests is increasingly well-described, additional caution has been recommended when considering pancreas transplantation. In order to better characterise the risks of SARS-CoV-2 transmission with pancreas transplantation, detailed data are needed on the timing of positive tests with respect to organ donation, along with other features that may indicate whether the donor's infection was evolving (e.g. serial polymerase chain reaction (PCR) cycle thresholds). Herein, we describe early outcomes after SPK transplantation from SARS-CoV-2 positive deceased donors in our unit since 23 March 2022.
Clinical Details: Donor 1 was a teenager with hypoxic brain injury, no preceding symptoms or signs of SARS-CoV-2 infection, but with consistently positive samples from the day of admission to the day of donation. The recipient was aged in 30s, dialysis-dependent, and with recurrent severe hypoglycaemic unawareness.
Donor 2 was aged in mid-20s with low body weight and intracranial haemorrhage. The donor had no previous symptoms or signs of SARS-CoV-2 infection, but became positive for SARS-CoV-2 RNA after initially testing negative. The recipient was aged in their 20s, dialysis-dependent, and had short stature making identifying size-matched organs a challenge.
As per UK guidance, discussions were held pre-transplant with transplant clinical colleagues, virologists, and the patients regarding the risks and benefits of implanting these organs. SPK transplantation was uneventful for both, and neither recipient received anti-SARS-CoV-2 prophylaxis. Both patients have been discharged from hospital with good function of the four grafts; recipient alternate day SARS-CoV-2 PCR tests for two weeks were all negative.
Conclusions: Pancreas transplantation from donors positive for SARS-CoV-2 within 48 hours of donation is reasonable if donors are appropriately risk-assessed for active, evolving infection.

PP44

PANCREATIC ALLOGRAFT THROMBOSIS: IMPLEMENTATION OF THE CPAT-GRADING SYSTEM IN A RETROSPECTIVE SERIES OF SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION.

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Background: Pancreatic graft thrombosis (PAT) is a major surgical complication, potentially leading to graft loss. The recently proposed Cambridge Pancreas Allograft Thrombosis (CPAT) grading system provides diagnostic, prognostic and therapeutic recommendations. The aim of the present study was to retrospectively assess CTA examinations performed routinely in SPK recipient to implement the CPAT grading system and to study its association with recipients' outcomes.
Methods: Simultaneous pancreas-kidney (SPK) transplant recipients (319 recipients of the 344 patients grafted from 2005 to 2019) underwent a routine computed tomography angiography (CTA) within the first 7 postoperative days. We retrospectively studied the incidence and grade of PAT using the CPAT grading system, correlating it to the patients' outcome.
Results: The analysis of CTA scans revealed signs of PAT in 215 patients (106 grade 1, 85 grade 2, 24 grade 3), while 104 showed no signs. These two groups of patients were compared. Demographic data of the two groups (thrombosis and non-thrombosis) did not show significant difference, except for the higher number of male donors in the thrombosis group. Pancreatic graft survival was significantly shorter in the thrombosis group. Graft loss due to PAT was significantly associated with grade 2 and 3 thrombosis (7/25 and 17/25, respectively) while it did not differ between recipients with grade 0 and grade 1 thrombosis.
Conclusions: The CPAT grading system was successfully implemented in a large series of SPK transplantations and proved applicable in clinical practice. Careful donor selection and an early protocol CTA might reduce the incidence of PAT and graft loss.

PP44a

EARLY POST-OPERATIVE RESULTS FROM 423 PANCREAS TRANSPLANTATION STRATIFIED ACCORDING DONOR'S AGE

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Background: Shortage of donors limits the numbers of pancreas transplantation (PTx) and when accept older donors remains unestablished. We evaluate the main post-operative complications dividing the population accordingly to the donor's age.
Methods: All PTx in every combination (SPK, SPLK, PAK, PTA) from 1996 to 2021 were considered. The population was divided in group 1 (0-10 years-old), group 2 (11-

45 years-old), group 3 (46-55 years-old). We analyzed: post-operative thrombosis rate, 30 days-rejection, reoperation, 90-days pancreas graftectomy and 90-days mortality.
Results: 423 PTx were performed: 243 (57.4) SPK, 28 (6.6) SPLK, 44 (10.4) PAK and 105 (24.8) PTA. There were 10 patients (pts) in the group 1, 379 pts in the group 2 and 34 pts in the group 3. The general characteristics of the donors are reported in the table 1. Donors stratified in the 3 age groups were significantly different with respect to PDRI (Group1vsGroup2vsGroup3), BMI (group1vsgroup2, p=0.04; group1vsgroup3, p=0.001) and cause of death (group1vsgroup2vsgroup3). Venous drainage was systemic in the 59.3% and exocrine was enteric in the 85.6% of PTx. Mean age was 40.3 ± 10.5 years, mean BMI was 23.2 ± 3.2 and cardiopathy was present in the 35.7% of the recipients. Mean cold ischemia time was 643.9 ± 134.6. Vascular thrombosis was present in 40 cases (9.4%) and was responsive to heparin infusion in 34 (%) cases in the other cases lead to pancreas graftectomy. Reoperation occurred in the 15.8% of the pts, pancreas graftectomy was performed in 24/423 pts (5.6%) and the 90-days mortality was 1.9% (8/423). With respect to the different outcomes in the different groups, the 90-days mortality was statistically different (p=0.03) between the group 2 and 3. The type of induction was statistically different in between the 3 groups (Tab.2).
Conclusions: PTx from donors of different age offers similar postoperative outcome, there is significant difference between 90-days post-operative mortality in the group from donor > 45 years old, thus the use of old donors should be evaluated accurately case by case. In this casistic PDRI, statistically different between group 3 and 1-2 could be useful to evaluate this chance, cause the other differences are already accounted in the PDRI. Larger and multicentric series are required for a better analysis.

Table 1 & Table 2

DONORS	Overall	Division by donor's age			p (1vs2)	p (1vs3)	p (2vs3)
		Group 1 (0-10 years old)	Group 2 (11-45 years old)	Group 3 (46-55 years old)			
N	423	10	379	34			
Age (mean ± SD)	28.3 ± 11.8	7.16 ± 2.9	27.45 ± 9.9	47.74 ± 1.26	**0.0001***	**0.0001***	**0.0001***
BMI (mean ± SD)	23.2 ± 3.5	19 ± 6.1	23.3 ± 3.27	24.3 ± 3	**0.04***	**0.001***	0.94
Sex male, N (%)	265 (62.6)	7 (70)	242 (63.8)	16 (47)	0.68	0.2	0.52
Cause of death					**0.02***	**0.02***	**0.04***
Anoxia	5	1	8	1			
Cerebrovascular/stroke	150	1	127	22			
Head trauma	267	8	243	11			
CNS tumor	1	0	1	0			
ICU (days, mean ± SD)	4 ± 3.8	2.2 ± 1.83	4 ± 3.88	4 ± 3	0.25	0.23	0.82
ACC (median, IQR)	0-2	0-1	0-2	0-2	0.78	0.87	0.85
Vasopressors Yes (%)	378 (89.4)	9 (90)	337 (88.9)	32 (94.1)	0.91	0.65	0.34
PDRI (mean ± SD)	1.16 ± 0.38	0.84 ± 0.15	1.1 ± 0.3	1.78 ± 0.26	**0.02***	**0.0001***	**0.0001***

RECIPIENTS	Overall	Division by donor's age			p (1vs2)	p (1vs3)	p (2vs3)
		Group 1 (0-10 years old)	Group 2 (11-45 years old)	Group 3 (46-55 years old)			
N	423	10	379	34			
Venous drainage							
- Portal N (%)	172/423 (40.7)	2/10 (20)	152/379 (35.9)	18/34 (52.9)	0.19	0.06	0.14
- Systemic N (%)	251/423 (59.3)	8/10 (80)	227/379 (64.1)	14/34 (41.1)			
Exocrine drainage							
- Enteric N (%)	362/423 (85.6)	10/10 (100)	343/379 (90.6)	31/34 (91.1)	0.31	0.45	0.89
- Bladder N (%)	39/423 (14.4)	0 (0)	36/379 (9.4)	3/34 (8.9)			
Age, (mean ± SD)	40.3 ± 10.5	41.2 ± 8.2	40.2 ± 10.8	40.3 ± 7.3	0.6	0.38	0.66
BMI (Kg/m^2), (mean ± SD)	23.2 ± 3.25	24.2 ± 2.3	23.6 ± 3.3	24.4 ± 2.7	0.21	0.71	0.99
Sex							
- M, N (%)	233/423 (55.1)	6/10 (60)	171/379 (45.1)	13/34 (38.2)	0.35	0.35	0.43
- F, N (%)	190/423 (44.9)	4/10 (40)	208/379 (54.9)	21/34 (61.8)			
Cardiopathy							
- Yes, N (%)	151/423 (35.7)	2/10 (20)	139/379 (36.7)	10/34 (29.4)	0.66	0.97	0.39
- No, N (%)	272/423 (64.3)	8/10 (80)	240/379 (63.3)	24/34 (70.6)			
n° of CCE (Chronic Evolutive Complications)	7/423 (1.65)						
- 0, N (%)	41/423 (9.6)	0 (0) 1/10 (10)	6/379 (1.6)	1/34 (2.9)	0.68	0.92	0.06
- 1, N (%)	174/423 (41.1)	6/10 (60)	36/379 (9.5)	4/34 (11.7)			
- 2, N (%)	180/423 (42.5)	3/10 (30)	147/379(38.7)	21/34(61.7)			
- 3, N (%)	21/423 (4.9)	0 (0)	170/379(44.8)	7/34 (20.6)			
- 4, N (%)			20/379 (5.3)	1/34 (2.9)			
Re-Transplantation							
No, N (%)	403/423 (95.3)	10/10 (100)	361/379 (95.2)	32/34 (94.1)	0.48	0.43	0.76
Yes, N (%)	20/423 (4.7)	0/10 (0)	18/379 (4.8)	2/34 (5.9)			
CIT (mean ± SD)	643.9 ± 134.6	595.6 ± 124.6	647.5 ± 136.3	621.2 ± 116.7	0.88	0.71	0.11
Induction with ATG							
- Yes, N (%)	174/423 (41.1)	4/10 (40)	154/379 (40.6)	19/34 (55.8)	**0.004***	**0.04***	**0.02***
- No, N (%)	249/423 (58.9)	6/10 (60)	225/379 (59.4)	15/34 (44.2)			
Vascular Thrombosis							
- No, N (%)	383/423 (90.5)	9/10 (90)	339/379 (89.4)	33/34 (97.1)	0.73	0.52	0.06
- Partial, N (%)	16/423 (3.8) 24/423 (5.7)	0 (0) 1/10 (10)	16/379 (4.2) 24/379 (6.4)	0 (0) 1/34 (2.9)			

PP45

THE COURSE OF COVID-19 INFECTION IN PATIENTS AFTER PANCREAS AND KIDNEY TRANSPLANTATION – A SINGLE - CENTRE OBSERVATION

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Background: Solid graft recipients are at an increased risk of serious complications and death.
Methods: Out of 130 outpatient recipients of pancreas grafts at our Clinic, 20 (15.73%) had a confirmed SARS-CoV-2 infection. Each patient had a different course of the disease and the forms of infection varied from mild to severe and lethal. According to recommendations, after confirmation of the infection mycophenolate mofetil (MMF) was withdrawn and the immunosuppression was based on steroids and a calcineurin inhibitor. In this study, we performed an analysis of the course of Covid-19 infection in patients after pancreatic transplantation. 20 pancreas recipients were confirmed covid 19 infection.
Results: 4 required hospitalization due to severe complications. Patients reported weakness, excessive intensity fatigue, shortness of breath with exertion, cough, periodically increased temperature. Weakness and fatigue persisted in these patients for about 6 weeks. In 2 cases there was a need for oxygen supplementation and empirical antibiotic. Mortality was 5% and there was one graftectomy. In no other cases, deterioration of pancreas graft, as well as kidney graft, was observed.
Conclusions: The course of SARS-CoV-2 infection in solid graft recipients is similar to the rest of the population. Because of immunosuppression, recipients are used to avoidance of the crowds and accustomed to mask obligation.

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THE COURSE OF ENCEPHALITIS IN A PATIENT AFTER PANCREAS AND KIDNEY TRANSPLANTATION - A CASE REPORT

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Background: Neuroinfections in patients after organ transplantation are a very dangerous complication. In the first period after the operation, it is associated with hospital infection or transfer of infection from the donor, in the later period - up to a year, these infections are usually opportunistic. According to the data from the literature, neuroinfection occurs in about 5-10% of cases after kidney transplantation, and the mortality rate is 44-77%. The course of infection depends on the immunosuppression used. The etiology is most often bacterial, viral, or fungal. Clinical symptoms vary from pain, and dizziness, to severe neurological symptoms.
Methods: We present the case of a patient who underwent pancreatic and kidney transplantation in May 2017 at the age of 62. Immunosuppression based on steroids, mycophenolate mofetil, tacrolimus and induction with polyclonal antibodies was used. In the early post-transplantation period, both transplanted organs functioned normally.

Results: In July 2022 - 62 months after the transplant - he was hospitalized in the Clinic due to headaches, balance disorders, insomnia, and memory disorders. In laboratory tests, high parameters of inflammation, normal pancreas, and kidney function, were shown. Head MRI revealed multifocal lesions in both hemispheres. Neurological diagnostics were deepened by examination of the cerebrospinal fluid. Immunosuppressive treatment was reduced to nothing except steroids. Broad-spectrum antibiotic therapy, antiviral and antifungal treatments were started. After 2 months, the patient's general and neurological condition improved. The calcineurin inhibitor was reintroduced. Antifungal and antiviral treatment was maintained. Follow-up head NMR showed further evolution and regression of the lesions. The nature of changes in MMR does not provide grounds for the diagnosis of PTLD or PML. Due to the positive EBV PCR result, and the nature of the brain lesions in the NMR examination, the suspicion of fungal or viral infection was raised despite the lack of positive cultures. The treatment has been continued, the patient's condition is gradually improving.
Conclusions: Currently, the survival time is 4 months, and despite the reduction of immunosuppression, the function of the transplanted organs is normal.

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PANCREAS ALLOGRAFT THROMBOSIS AS A POST-COVID-19 COMPLICATION IN DIABETIC PATIENT

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Background: The SARS-CoV-2 pandemic has caused a huge overload onthe healthcare system worldwide [1]. From March 4th 2020 until December, 07th 2021 the total number of COVID-19 cases in Poland reched 3,684,671 million. According to the Polish Ministry of Health 85,700 infected patients died, most of them had been suffering from concurrent disease. [2] The mortality rate from COVID-19 in Polish population is ~ 2.5%. An increase of thrombotic and thromboembolic complications has been associated with COVID-19 in both arterial and venous systems. [3,4] Patients after transplantation suffering from COVID-19 are at a higher risk of mortality (42-24%) and complications than the average population. [5]
Methods: Hospital database analysis and literature search
Results: Recently, in our Center, there was a case of a PTA recipient with diabetes t1 that developed venous and arterial thrombosis 4 months after COVID-19, resulting in graft necrosis and finally in pancreas graftectomy [figure A-F]. Our 6-year post-PTA patient had no history of thromboembolism or other risk factors apart from diabetes t 1 and a history of COVID-19. Earlier, in 2020 and 2021, 2 cases of infarction of a transplanted kidney in patients suffering from COVID-19 were described. Moreover, both cases occurred in obese transplant recipients with diabetes t 1. The first case - a man with DM t1 13 years after kidney and pancreas transplantation who had a segmental infarction of the kidney [6], and the second case was a woman with DM t1 6, 5 months after kidney transplantation, who lost the graft as a result of a renal artery infarction. [7] Identifiable risk factors linking these cases are the post-transplant status for t1 diabetes and obesity.

Conclusions: Transplant patients who have experienced COVID-19 should be carefully monitored for the occurrence of graft arterial and vein embolism. Early detection of these complications in patients after organ transplantation gives an opportunity to save the organ. Thromoprophylaxis with low molecular weight heparin is highly important and should be continued in high-risk patients (obese, with persistent d-dimer levels> 1000) for a minimum of 2 weeks (preferably 4-6 weeks) after reaching the convalescent status.

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PREGNANCY AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

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Background: Renal impairment, secondary to diabetic nephropathy, may result in gonadal insufficiency with infertility. SPKT can restore fertility in patients with DT1 and ESKD and as such, successful pregnancy is possible
Methods: hospital database analysis
Results: 29 yo F with a history of T1 DM diagnosed at the age of 12, complicated by retinopathy and nephropathy (which required RRT). She underwent SPKT 2 years earlier. There were 4 HLA mismatches. Induction immunosuppressive therapy included ATG and Tac, MMF, and Pred. She had no surgical complications and immediately achieved normoglycaemia and good renal allograft function, with serum crea of 1,0 mg/dl on discharge day.
Pregnancy was planned, MMF was changed to AZA. There was good function of both grafts with serum crea of 0,8-1,2 mg/dl with fasting blood glucose of 88 mg/dl. She was diagnosed with pregnancy-induced hypertension at week 12 and received methyldopa. Multiple scans for fetal well-being were performed, and no fetal anomalies were found. Tac levels were stable throughout pregnancy and within the range of 6-8 ng/ml. Blood glucose monitoring, FPG and HbA1c levels were in the normal throughout pregnancy. OGTT screening was negative for GDM.
Serum crea increased throughout the pregnancy with 1,6 mg/dl at the delivery. She underwent elective C-section at week 32 due to preeclampsia. BP was 200/120 mmHg, with poor reaction to drugs. The procedure was uncomplicated, and no deterioration in grafts function was observed.
She delivered a female infant who had APGAR scores of 8-10 at five and ten minutes, respectively. Birth weight was 1900 g, which was appropriate for gestational age Babygirl was healthy. Following delivery, our patient experienced progression of hypertension and required the addition of amlodipine. At 24 month followup, she has stable function of both grafts.
Conclusions: Compared to other solid organ recipients SPKT females have similar rates of spontaneous miscarriage and therapeutic abortion, but higher rates of preterm delivery, low birth weight, hypertension, infection, pre-eclampsia, acute rejection, and graft loss in later years. Risks are reduced if pregnancy is planned and if the graft is functional at least one-year after SPKT without evidence of rejection; with normal BP and stable immunosuppression doses.