

# PANCREAS

**Conclusions:** Non-contrast-enhanced MRA with IFIR combined with ASL provide accurate assessments of vascular anatomy, perfusion and complications following simultaneous pancreas-kidney transplantation, all without the requirement for contrast agents. These imaging modalities offer the benefits of non-invasiveness, safety and precision in examining patients undergoing simultaneous pancreas-kidney transplantation, making them especially advantageous for long-term follow-up in patients with renal insufficiency.

**CITATION INFORMATION:** Wen J., Luo Y., Dong J., Li M., Lu B., Sun X. Assessment of Vascular Anatomy, Perfusion and Complications in Simultaneous Pancreas-Kidney Transplant Recipients via Non-Contrast-Enhanced Magnetic Resonance Imaging AJT, Volume 25, Issue 8 Supplement 1

**DISCLOSURES:**

## Abstract# P3.11.37

### Effects of Modified Splenic Arteriovenous Fistula Formation at the Tail of the Transplanted Pancreas on Thrombosis Prevention in Simultaneous Pancreas-Kidney Transplantation

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**Purpose:** To investigate the clinical utility of a modified technique for creating a splenic arteriovenous fistula at the tail of the transplanted pancreas to prevent thrombosis during simultaneous pancreas-kidney transplantation (SPKT).

**Methods:** Between January and September 2024, eight cases of modified splenic arteriovenous fistula formation at the tail of the transplanted pancreas were performed at our institution, consisting of seven males and one female, with a median age of 42.5 years (range: 33-53 years) and a median body mass index (BMI) of 25.2 kg/m<sup>2</sup> (range: 20.7-26.6 kg/m<sup>2</sup>). Among these, two were diagnosed with type 1 diabetes and six were diagnosed with type 2 diabetes. Exocrine drainage of the pancreas was performed using intestinal diversion, and venous return surgery was performed with the transplanted kidney positioned in the left iliac fossa and the transplanted pancreas located in the right abdominal cavity. The median age of donors was 29 years (range: 20.2-33.5 years), with a median BMI of 20.8 kg/m<sup>2</sup> (range: 19.5-22.5 kg/m<sup>2</sup>); the blood types of the donors and recipients were identical. Following the surgery, Doppler ultrasound and contrast-enhanced CT angiography were performed to assess the incidence of thrombosis in the transplanted pancreas.

**Results:** None of the eight cases exhibited thrombosis in the transplanted pancreas, nor were there any severe complications, and graft function was successfully restored. One patient demonstrated delayed graft function (DGF), one experienced bleeding at the site of the transplanted pancreas, another had perirenal hemorrhage, one exhibited poor incision healing in the transplanted pancreas, and one required temporary insulin transition two days post-surgery.

**Conclusions:** The modified technique for creating a splenic arteriovenous fistula at the tail of the transplanted pancreas effectively reduced thrombosis after pancreas-kidney transplantation. However, further validation through multicenter studies with larger sample sizes are warranted.

**CITATION INFORMATION:** Li M., Wen J., Dong J., Sun X. Effects of Modified Splenic Arteriovenous Fistula Formation at the Tail of the Transplanted Pancreas on Thrombosis Prevention in Simultaneous Pancreas-Kidney Transplantation AJT, Volume 25, Issue 8 Supplement 1

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## Abstract# P3.11.38

### Should Robotic Simultaneous Pancreas-Kidney Transplantation Become the New Standard for Type 2 Diabetes and Obesity? A Single-Center Retrospective Analysis

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**Purpose:** This study aims to analyze our single-center experience with simultaneous pancreas-kidney (SPK) transplantation, comparing outcomes in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Additionally, we present findings from, to the best of our knowledge, the largest cohort of robotic SPK (RSPK) transplants reported to date.

**Methods:** This retrospective analysis includes 190 SPK transplants performed between 2015 and 2023. Descriptive and multivariable analyses were conducted. Risk factors for patient and graft survival were assessed using Kaplan-Meier estimates and time-dependent Cox regression models.

Potential risk factors examined included age, race, gender, body mass index (BMI), diabetes type, C-peptide levels, dialysis status, transplant year, and graft status.

**Results:** Of the 190 SPK transplants, 168 (88.4%) were performed using an open approach, while 22 (11.6%) were robotic. The proportion of transplants in patients with T2DM increased from 10% (2015-2017) to 50.9% (2021-2023) (p = 0.001).

Overall, T2DM patients were older and had higher BMI and C-peptide levels (p < 0.0001). Among patients with BMI > 30 kg/m<sup>2</sup>, RSPK was performed in 18 out of 22 cases (82%). Weight change over time was significant, decreasing in the first month post-transplant and increasing slightly thereafter. After adjusting for gender, age, and diabetes type, a significant weight change remained over time. C-peptide levels were categorized into tertiles: low (0.01-0.1 ng/mL), intermediate (0.2-3.0 ng/mL), and high (> 3.0 ng/mL). Longitudinal analysis revealed no statistically significant differences in weight gain trajectories across C-peptide tertiles (p > 0.05). This non-significant association persisted after adjustment for baseline weight in multivariable modeling. Censored pancreas graft survival was 91% at 1 year and 80% at 5 years, while kidney graft survival was 98% at 1 year and 85% at 5 years. Overall patient survival was 97% at 1 year and 80% at 5 years. None of the evaluated risk factors, including diabetes type and C-peptide levels, were found to be significant predictors of patient survival. Additionally, mortality in our cohort was predominantly attributed to diabetic-related complications, underscoring the importance of early intervention in the management of diabetic disease, to achieve long-term survival and clinical outcomes.

**Conclusions:** SPK transplantation in the T2DM population has shown to be a safe and effective approach, yielding outcomes comparable to those in T1DM patients. RSPK was preferentially performed in patients with higher BMI, yet outcomes remained comparable to those in patients with lower BMI.

**Table 1.** Recipient characteristics stratified by Diabetes Mellitus type.

Characteristics	All patients (n=190)	T1DM (n=132)	T2DM (n=58)	P value
Age (y), mean ± SD	44 ± 9.4	42.2 ± 9.2	48.1 ± 8.9	0.0001
Weight, (kg), mean ± SD		81.3 ± 21.9	85.1 ± 19.8	
Male gender, n (%)	106 (55.7%)	75 (56.8%)	31 (53.4%)	0.6667
BMI (kg/m <sup>2</sup> ), mean ± SD	29 ± 6.6	28.5 ± 7	30.1 ± 5.5	0.0154
Ethnicity and race, n (%)				0.0909
- African American	76 (40%)	48 (36.3%)	28 (48.2%)	
- Hispanic	63 (33.1%)	42 (31.8%)	21 (36%)	
- Caucasian	36 (18.9%)	31 (23.4%)	5 (8.6%)	
- Other	15 (7.9%)	11 (8.3%)	4 (6.8%)	
ESRD on dialysis, n (%)	162 (85.2%)	110 (83.3%)	52 (89.6%)	0.2576
Co-morbidities, n (%)				
- Hypertension	169 (88.9%)	116 (87.8%)	53 (91.3%)	0.8285
- Hyperlipidemia	55 (28.9%)	35 (26.5%)	20 (34.4%)	0.2354
- Low Function & Potential HF (EF<45%)	16 (8.42%)	11 (8.3%)	5 (8.6%)	0.7916

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## Abstract# P3.11.39

### Outcomes of Simultaneous Kidney and Pancreas Transplantation in Patients with Type 2 Diabetes Mellitus: A Single-Center Experience

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**Purpose:** Simultaneous pancreas and kidney transplantation (SPK) is a well-established treatment for patients with end-stage renal disease (ESRD) and type 1 diabetes mellitus (T1DM). However, its efficacy in patients with type 2 diabetes mellitus (T2DM) remains less well-defined, as the criteria for optimal patient selection and favorable outcomes have yet to be clearly established. This study aims to assess the outcomes of SPK in patients with T2DM at our institution.

**Methods:** A total of 27 patients with T2DM and chronic kidney disease (CKD) underwent SPK transplantation between 2020-2024. Demographic and clinical data were collected, and all procedures were performed according to standardized protocols, utilizing systemic venous and enteric duodenal drainage. Postoperative outcomes, including graft function and complications, were evaluated. Patients were followed for up to five years post-transplantation.

**Results:** The study cohort included 20 men and 7 women, with a median age of 49 years (range: 30-60). The majority of patients required hemodialysis (70%) or peritoneal dialysis (19%) prior to transplantation. The median body mass index (BMI) was 27 kg/m<sup>2</sup> (range: 19-33), and the median weight was 84 kg (range: 51-107). Preoperative metabolic parameters included a median fasting C-peptide level of 1.93 pmol/mL (range: 0.21-6.49) and a median HbA1c of 7.0% (range: 4.7-14.6). The median daily insulin requirement was 30 units (range: 4-90). The median

postoperative length of stay was 10 days (range: 6-25). Pancreas graft thrombosis occurred in 10% of patients, necessitating surgical removal. Other complications, including bleeding and abscess formation, required re-laparotomy in 16% of cases. More than half of the patients experienced post-transplant complications requiring hospital readmission. Among patients with preserved pancreas graft function, all demonstrated improved blood glucose control, with none requiring chronic insulin therapy postoperatively. HbA1c levels decreased in 81% of patients, reaching a median of 5.5% (range: 4.7-7.1), while the remaining 19% experienced a slight increase to a median of 6.1-6.5%. Fasting C-peptide levels increased in 70% of patients and decreased in 30%. Kidney graft function remained stable in all patients, with no cases of delayed graft function or graft loss. Additionally, the waiting time for SPK was significantly shorter compared to kidney transplantation alone in our region: 80% of patients received their transplant within three years, 63% within two years, and 26% within one year.

**Conclusions:** Simultaneous pancreas and kidney transplantation (SPK) in patients with T2DM provides significant advantages, including shorter wait times for high-quality kidney grafts, sustained blood glucose control without the need for insulin therapy, and stable kidney graft function. However, this approach carries a higher risk of postoperative complications, leading to increased rates of hospital readmission and the need for surgical interventions compared to kidney transplantation alone.

**CITATION INFORMATION:** Bachul P., Juengel B., Kyeso Y., Perez-Gutierrez A., Cimen A., Suah A., Gaffan A., Habbouche J., Krishnamoorthy S., Cunningham P., El Kassir Y., Josephson M., Concepcion B., LaMattina J., Fung J., Barth R., Witkowski P. Outcomes of Simultaneous Kidney and Pancreas Transplantation in Patients with Type 2 Diabetes Mellitus: A Single-Center Experience AJT, Volume 25, Issue 8 Supplement 1

**DISCLOSURES:** J. Habbouche: None.

### Abstract# P3.11.40

#### Optimizing Immunosuppression for Beta Cell Replacement: Efficacy and Tolerability of Belatacept with Low-Dose Tacrolimus

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**Purpose:** Significant progress in beta cell replacement therapy has been made with the introduction of stem cell-derived islet transplantation, offering a potential functional cure for type 1 diabetes mellitus (T1DM). However, tacrolimus toxicity remains a major barrier to widespread clinical adoption. This study evaluates a strategy of minimizing tacrolimus exposure through belatacept infusions to improve the tolerability and effectiveness of immunosuppression following islet transplantation.

**Methods:** We studied 14 patients with T1DM who underwent cadaveric pancreatic islet transplantation. Induction therapy included Thymoglobulin for all patients, while maintenance immunosuppression consisted of monthly belatacept (5 mg/kg) with low-dose tacrolimus (target: 3-5 ng/mL). Ten patients (67%) received this regimen de novo at transplantation, while four (33%) transitioned from tacrolimus/antimetabolite therapy due to complications such as rising creatinine, chronic diarrhea, or increasing donor-specific antibodies (DSA).

**Results:** Belatacept (5 mg/kg monthly) with low-dose tacrolimus effectively prevented de novo DSA, antibody-mediated rejection (AMR), and islet graft loss in all 14 patients (100%) over a 14-month follow-up, compared to only 33% (2/6) in a historical cohort treated with tacrolimus and an antimetabolite. However, belatacept required dose adjustments in 7 patients (50%), including discontinuation in 2 and reduction to 2.5 mg/kg monthly in 5 patients (36%) due to adverse events such as chronic neutropenia, skin rash with mouth ulcers, Epstein-Barr virus reactivation, recurrent norovirus, Clostridium difficile infection, and urinary tract or respiratory infections. To mitigate these risks, belatacept was proactively reduced to 2.5 mg/kg monthly in the remaining 7 patients, leading to resolution of infectious and toxic complications while preserving islet graft function in all cases.

**Conclusions:** Belatacept combined with low-dose tacrolimus effectively prevents DSA, AMR, and islet graft loss. However, reducing the belatacept dose to 2.5 mg/kg monthly is critical for minimizing toxicity and infectious complications, underscoring the need for a carefully balanced immunosuppressive strategy in islet transplantation.

**CITATION INFORMATION:** Wojcik N., Juengel B., Appelbaum N., Juszczak A., Basto L., Escobedo M., Wang L., Tibudan M., Klein T., Perea L., Barth R., Fung J., Witkowski P. Optimizing Immunosuppression for Beta Cell Replacement: Efficacy and Tolerability of Belatacept with Low-Dose Tacrolimus AJT, Volume 25, Issue 8 Supplement 1

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### Abstract# P3.11.41

#### Apoptotic BMSCs Reduces Grafted Islets Apoptosis through the Holo-LCN2/Slc22a17/Fe<sup>3+</sup> Axis

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**Purpose:** Early apoptosis of grafted islets is a critical issue that affects the efficacy of islet transplantation. BMSCs possess anti-inflammatory, antioxidant, tissue repair, and immune-regulating properties. The protective effect of BMSCs on islet cells is largely attributed to their potent paracrine effects. Pre-conditioning BMSCs with hypoxia or other agents before stem cell therapy can enhance their protective function. This study investigates the role of apoptotic BMSCs in alleviating early apoptosis of transplanted islets and explores the underlying molecular mechanisms.

**Methods:** 1. Extract rat BMSCs and treat them with Staurosporine (STS) to construct a stable apoptosis-induced BMSCs (BMSCs-STs) system. Then detect the apoptosis levels of BMSCs. The conditioned medium (CM) from both BMSCs and BMSCs-STs is then collected. 2. Use SD rats and perform retrograde infusion collagenase P into the common bile duct for in situ perfusion. Digest it at 38°C for 17 minutes. Islets are purified using discontinuous density gradient centrifugation. 3. Intraperitoneally inject streptozotocin (STZ) into rats to induce blood glucose levels exceeding 16.7 mM/L for three measurements. The apoptotic BMSCs are co-transplanted with islets under the renal capsule of diabetic rats. From day 0 to day 14 after transplantation, blood glucose and body weight levels are measured. Glucose tolerance tests are performed on days 7 and 14 to assess the function of the grafts. At day 7 or 14 post-transplantation, tissue samples are collected for insulin immunohistochemical staining. 4. Construct an in vitro model of islet cell apoptosis during transplantation by stimulating rat insulinoma (INS-1) cells with STZ. Pre-treat INS-1 cells and islet cells with BMSCs CM and BMSCs-STs CM for 24 hours, then treat INS-1 with 3mmol STZ. Observe the regulatory effects of both CMs on  $\beta$ -cell apoptosis. 5. Using proteomics and bioinformatics techniques, analyze the differentially expressed proteins in BMSCs-STs CM and BMSCs CM, and then screen for the anti-apoptotic protein holo-LCN2, followed by further in vitro validation of its anti-apoptotic phenotype.

**Results:** 1. BMSCs-STs CM more effectively alleviates apoptosis in transplanted islets, increases islet cell survival in vivo, and preserves the insulin secretion capacity of islet cells. 2. BMSCs-STs CM, relative to BMSCs CM, significantly reduces STZ-induced apoptosis, decreases apoptosis in INS-1 cells and primary islets, and confirms that the paracrine effect is the primary mechanism through which stem cell CM exerts its protective effects. 3. Holo-LCN2 may protect INS-1 and primary islets by binding to the membrane protein SLC22A17 and facilitating the transport of Fe<sup>3+</sup>.

**Conclusions:** Apoptotic BMSCs, when co-transplanted with islets under the renal capsule of diabetic rats, can more effectively inhibit the apoptosis of the grafted islets. CM from apoptotic BMSCs, which contains the effective anti-apoptotic component holo-LCN2, pre-treated INS-1 cells and was able to inhibit STZ-induced apoptosis. This anti-apoptotic function is Fe<sup>3+</sup> dependent.

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### Abstract# P3.11.42

#### ISL1 Suppresses Apoptosis by Deubiquitinating GRP78 through USP18 to Improve Islet Cells Survival in the Early Stages of Transplantation

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**Purpose:** The early apoptosis of transplanted islet often leads to poor efficacy of islet transplantation. ISL1 is one of the key transcription factors in islet cells. To better understand the effect of ISL1 in the apoptosis of transplanted islets, we investigated whether the level of cell apoptosis in islet cells with increased ISL1 expression was reduced and the specific mechanism involved.

**Methods:** In vivo, ISL1 conditionally overexpressing rats and adenovirus were used to extract and construct ISL1 overexpressing islet cells, which were transplanted under the renal capsule of diabetes rats. Immunohistochemistry, immunofluorescence staining and quantitative morphometry were used to detect the apoptosis level in the transplanted islets. In the islet cell injury model constructed by STZ in vitro, Western blotting, RT-qPCR, and flow cytometry were used to detect the effect of ISL1 expression level changes on islet cells apoptosis. In addition, the relevant mechanisms of ISL1 on the apoptosis of transplanted islets were elucidated through CHIP-seq, RNA-seq, and IPMS.

**Results:** Our report states that increasing the expression level of ISL1 in islet cells significantly reduces apoptosis compared to the control group. CHIP-seq and RNA-seq analysis of isolated islet cells showed that ISL1 can directly bind to the USP18 promoter region, promoting USP18 transcription. Subsequently, IP-MS results showed that USP18 could interact with GRP78, GRP78-K78 can induce deubiquitination of GRP78, thereby inhibiting pancreatic cell apoptosis.