

## Slovak first islets after kidney allotransplantation in cross border cooperation and mentorship from Czech's IKEM-Prague

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### Abstract

Close cooperation between transplant centers and mentorship are essentials in establishing successful new transplant program. Up today, there is no transplant center in Slovak Republic providing active pancreas or islets transplant programs. Historical background of Slovak and Czech nations and excellent personal relationships between transplant professionals led to close cross border cooperation in the field of transplantation. We report our case of Slovak first islets allotransplantation from a brain dead multiorgan donor after living donor kidney transplantation in cross border cooperation between Slovak and Czech transplant centers and mentorship from IKEM-Prague. Surgical procedures have been performed in The University Hospital Kosice, Slovak Republic. Islets isolation procedure has been performed in The Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic. Transfer of organs and mentoring medical staff between centers was arranged by Air Transport due to distance between centers - 658 km. Overall time from pancreas procurement to islets transplantation was 10 h 40 min.

**Keywords:** Islets of Langerhans, Kidney, Transplantation, Mentorship, Cooperation

### Introduction:

Islet transplantation has long been a sought-after solution for restoring glucose homeostasis in diabetes caused by islet b-cell loss in the autoimmune attack of type 1 diabetes (1). Although the ability to achieve normal glucose control in diabetic rodents with islet transplantation was first described decades ago, translating this success to humans has been difficult (2). Starting in 1974, several centers attempted human islet transplantation, with 445 recipients receiving islets between 1974 and 2000. Most of these recipients also received a kidney transplant, either before or at the same time as the islet transplant. Analysis of reported cases between 1990 and 2000 showed that only 19% of patients were off insulin for more than 1 week, and at 1 year follow-up only 11% of recipients were insulin independent (3). Interest in allogeneic islet transplantation exploded when researchers at the University of Alberta, Edmonton, Canada, reported for the first time that

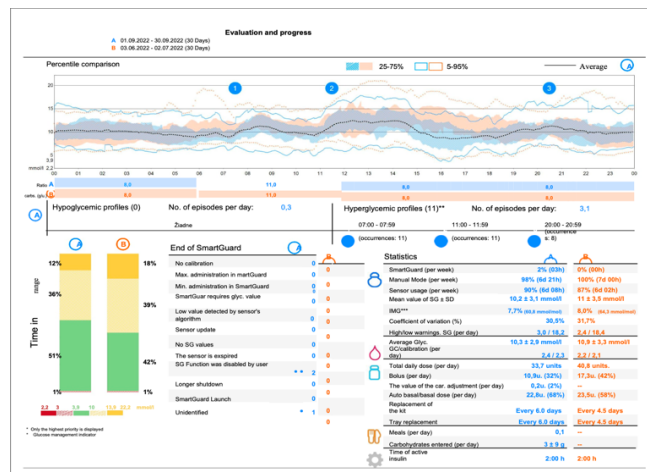
diabetes could be consistently reversed in patients by isolated islet transplantation. In the early trials of isolated islet transplantation, it was important to show that the procedure was safe for the recipient (4). The most feared potential complications include bleeding and portal vein thrombosis (5). Alternatively, the procedure can be performed via a small laparotomy to gain access to an umbilical vein, through which a catheter can be advanced into the main portal vein for islet infusion. The umbilical vein is then ligated, essentially eliminating the potential for bleeding (6). The surgical approach allows anticoagulation to be administered without the risk of bleeding from a puncture site in the liver parenchyma, although general anesthesia is usually required. The relative safety advantage of islet transplantation compared with whole pancreas transplantation was clear when the two approaches were compared. Reported major complications, including bleeding requiring transfusion and reoperation, were more

common in the whole organ group, although a number of minor complications were more common in the islet transplant group, including immunosuppression-related toxicity (mouth ulcers, oedema), periportal hepatic steatosis and mild liver function test abnormalities (7).

### Case report:

**Recipient characteristics:** 38-year-old woman, BMI 28,7 with a history of type 1 diabetes mellitus (T1D) since the age of 8 years, in the stage of chronic complications, has been followed at the diabetes outpatient clinic of the University Hospital in Kosice since 2016. Despite treatment with an insulin pump with a hybrid closed loop system, poor metabolic compensation persisted. The patient presents with chronic complications of T1D such as

hypoglycemia unawareness phenomenon, proliferative diabetic retinopathy, diabetic neuropathy, cardiac autonomic neuropathy, and G5A3 KDIGO diabetic kidney disease with the need for hemodialysis treatment between February 2022 and September 2023. As a result of chronic kidney disease, the patient suffered from secondary arterial hypertension, hyperlipoproteinemia and hyperparathyroidism. In 2018, during her first pregnancy, she experienced pre-eclampsia and underwent hysterectomy a week after delivery due to postpartum metrorrhagia with hypovolemic shock. During the period of hemodialysis, the metabolic compensation of T1D significantly worsened, with marked variability in glycemic control and the occurrence of frequent hypoglycemia.



**Figure 1:** documents the continuous glucose monitoring during the hemodialysis period, which confirms only 42-51% of time in range (3.9-10.0 mmol/l) with 48-57% of time above range (over 10,0 mmol/l). On the other hand, because of the risk of hypoglycemia, insulin pump was suspended for 2-9 hours per day.

The patient was considered for kidney transplantation. Due to brittle diabetes and hypoglycemia with a phenomenon of unawareness of warning signs, transplantation of Langerhans' islets was also considered. As such treatment is not available in Slovakia, we approached the Institute for Clinical and Experimental Medicine in Prague, Czech Republic, for cooperation and mentorship.

### Kidney transplantation – September 5th 2023 – University Hospital Kosice

- Hand assisted retroperitoneoscopic living donor left-side nephrectomy
  - o genetically related donor
  - o HLA mismatch (1/1/1 – compatibility index 13)
  - o CMV status - positive donor - positive recipient
- Minimally invasive kidney transplantation
  - o WIT: 1min. 37 sec.
  - o CIT: 3h 37 min.
  - o PGF - eGF 1,25 ml/s

The immunosuppression protocol consisted of induction therapy including depleted polyclonal antibody – anti-thymocyte globulin at a cumulative dose of 5.3 mg/kg and methylprednisolone 500mg (D0, D1 and D2). The first dose was given before reperfusion, followed by maintenance treatment based on tacrolimus, mycophenolat mofetil and corticosteroids. The patient received antibiotic prophylaxis and antithrombotic prophylaxis based on low-molecular-weight heparin.

### Multiorgan procurement – September 8th 2023 – University Hospital Kosice

Donor characteristics: 28 y. o. male, BMI 27,8, brain death after isolated craniotraumata (DBD), ICU stay >36h, without previous medical history. During standard multiorgan procedure, Lungs, Heart, Liver, Pancreas, Kidneys and Iliac Vessels have been procured.

Islets isolation procedure - September 8th 2023 – IKEM, Prague  
After the delivery to the pancreatic laboratory in Prague, 110g pancreas was filled and distended by 100ml of 4 degree Celsius cold

collagenase solution (Nordmark pharma GmbH). The distended organ was divided into 12 pieces and placed in the digesting chamber. After 20 min of digestion, islets were released and collected into the bag with UW solution. Cobe 2999 was used to purify islets in a continuous Biocoll gradient. Islets were counted using Isletnet

(www.isletnet.org), the web environment using artificial intelligence. Altogether, 314 333 islets corresponding to 214 901 islet equivalents were diluted in the 160ml transplant medium. (CMRL 1066, human albumin and HEPES solutions). (Pictures 1-3)



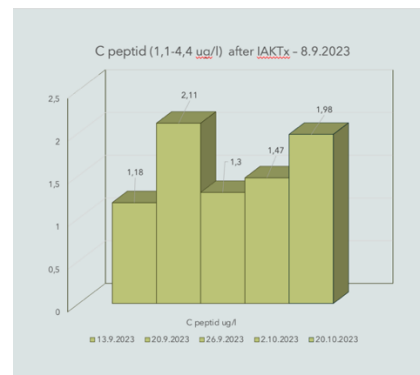
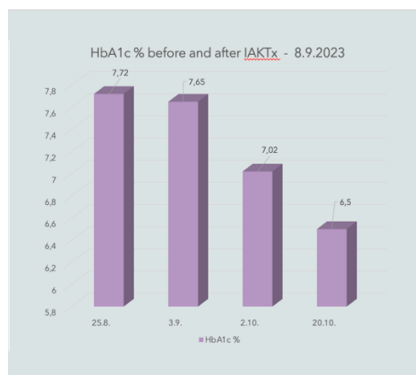
### Islets Transplantation – September 8th 2023 – University Hospital Kosice

- Open surgical procedure - upper medial minilaparotomy
- Islet solution was infused via umbilical vein to the liver portal venous system
- Under radiological control – C-arm skiascopy
- Portal vein pressure monitoring (max. 25 mmHg)



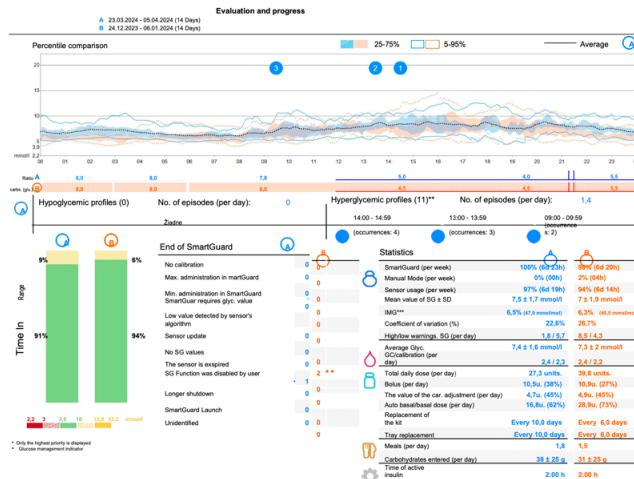
**Results:** Post transplant course after LDKTx was without complications, a small asymptomatic lymphocele has spontaneously resorbed in 1 month after procedure. After Langerhans' islets transplantation, there was a 1.05% decrease in HbA1c DCCT after

7 months (7.65% vs 6.5% DCCT). C peptide levels increased from unmeasurable values before transplantation to values of 1.18-2.11 µg/l after transplantation (normal 1.1-4.4 µg/l).



There has been a significant improvement in glycaemic variability with a reduction in hypoglycaemia. Patient no longer needs to cover meals with lower carbohydrate units with bolus insulin. Figure

2 shows continuous glucose monitoring 3 months (Figure B) and 7 months (Figure A) after transplantation of Langerhans' islet with achievement of time in range of 91-94%.



**Conclusion:** Our case report of the first islets after kidney transplantation in Slovak Republic, in the country without active pancreas/islets transplant program shows good example of successful cross border cooperation despite logistic, coordination and financial difficulties and excellent mentorship of well experienced partner transplant center IKEM Prague. After short postoperative follow up, it is not possible correctly form conclusions, but personal patient valuation after transplantation is: I have new better quality of life.... Optimal metabolic compensation will ensure prevention of progression of chronic complications and protection of the transplanted kidney. Of course, longer follow up to exactly confirm the results is essentially needed. We strongly believe that this is the way how we could offer alternative treatment option for our diabetic patients also in the future.

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