**Forum Nephrologiczne. 2018, 11, 1, 43-49.**

# Pancreatic islets after kidney transplantation – Two case report.

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## Abstract

Simultaneous pancreas and kidney transplantation is the best therapeutic option for patients with poorly controlled type 1 diabetes, stage five chronic kidney disease and other secondary diabetic complications. However, when a pancreas transplant is contraindicated or unavailable, pancreatic islet transplantation is an alternative minimal invasive procedure. It allows for improved and easier glucose control, prevents progression of secondary diabetic complications and improves quality of life. We would like to present two patients who received an islet transplant after a kidney transplantation which led to improved glucose control, lower A1c, improved quality of life with stable and good kidney graft function.

## Case 1.

43-year-old male patient with T1DM since 5 years of age, with a history of long-term hypertension and end stage renal disease due to diabetic nephropathy, on hemodialysis since age 38, was admitted for simultaneous pancreas and kidney transplantation (SPK). Chronic kidney disease (CKD) was diagnosed in 2006. One year later chronic hemodialysis was started through an A-V fistula on the right forearm and subsequently through the vascular prosthesis on the left forearm. At the time of evaluation for kidney and pancreas transplantation, the patient was diagnosed with multiple diabetic complications e.g. macro- and microangiopathy. In a coronary angiography performed three years ago, diffuse atherosclerotic lesions in all vessels were found, however hemodynamically significant only in the right coronary artery, where 3

stents were implanted. In addition, due to atherosclerosis of the lower limbs, one stent to each vessel of both thighs was implanted. In the pre-transplant CT scan of the abdominal cavity and pelvis, extensive calcifications in arterial vessels were found, including common, external and internal iliac arteries, bilaterally. The patient had no hemodynamically significant changes in the carotid and vertebral arteries. He had surgery for cataract of the left eye and bilateral diabetic retinopathy. There were sensory losses in the lower limbs in the course of diabetic neuropathy. Glycemic control was unsatisfactory, with A1c between 10-12%, despite treatment with an insulin pump. The average daily insulin dose was about 40-50 units. The patient experienced several episodes of severe hypoglycemia per month, due to development of hypoglycemia unawareness, despite the fact that he tried to prevent hypoglycemic attacks by maintaining an elevated level of glucose in the serum and taking lower than optimal doses of insulin. There were no other comorbidities. The patient had already undergone subtotal parathyroidectomy while on dialysis. Family history was non-significant. Since 2005, the patient stopped smoking. The patient weighed 73 kg and the BMI was 23.3 kg/m2. Patient underwent pancreas and kidney transplantation on July 18, 2012. The donor was a 19 year-old man who died due to a cranial-cerebral injury. Donor blood type A was compatible with the recipient's blood type. The degree of match in histocompatibility complex (HLA – human leukocyte antigen) included only 1 compatible antigen in group A(5 incompatible antigens). PRA(panel of reactive antibodies) measured by solid-phase assays was 0.

A four-drug combination of immunosuppression was used: glucocorticosteroids, tacrolimus (Prograf), mycophenolate mofetil (CellCept), with Thymoglobulin as an induction. The kidney was transplanted into the right iliac fossa by anastomosing the graft vessels with the external iliac vessels of the recipient. The urethra was implanted into the urinary bladder on the "double J" urethral catheter. Next, the pancreas was implanted by anastomosing the portal vein with the superior mesenteric vein of the recipient, and arterial vessels of the pancreas using the conduit created from donor's common iliac artery. While the intestinal anastomosis was performed, the venous anastomosis became thrombotic. Attempts to restore the blood flow through anastomosis between mesenteric vein of the recipient and the donor's portal vein proved to be ineffective and the transplanted pancreas was removed. Immediately after the procedure, diuresis was observed (over 1200 ml per day) with reduction of plasma creatinine level. The patient did not require hemodialysis. The postoperative course was uncomplicated with creatinine level 1.0 mg/dl at discharge.

After kidney transplantation, the patient still had problems with maintaining normal blood glucose control, and his HbA1c was maintained at 12%. Due to advanced atherosclerotic changes in arterial vessels and a high risk of thrombosis, the patient did not qualified for re-transplantation of the pancreas. Patient did however qualify for pancreatic islet transplantation, in order to improve glycemic control and protect the transplanted kidney from the development of diabetic nephropathy and progression of atherosclerotic lesions in the blood vessels. Because the patient was already taking immunosuppressive medications after kidney transplantation, pancreatic islet infusion, as a minimally invasive procedure, came with a relatively low risk of complications with the potentially high benefit of stopping the progression of diabetic complications. Due to the very poor glycemic control, which did not promise good cooperation, especially with a limited prospect of achieving insulin independence, the patient had to demonstrate effective collaboration with the diabetologist in order to reach an A1c level of 9% or below.

After a few months, the patient had the required A1c level and the pancreatic islet transplantation was performed on October 13th, 2014, with an amount of 306,401 IEQ (IEQ - islet equivalents). The donor, was a 51-year-old man who died of a cranial-cerebral injury, and had matched blood type A. This time all antigens in the HLA complex were incompatible (in the recipient no anti-HLA antibodies were found in solid-phase assays), and one incompatible antigen repeated, which was also present in the kidney donor. Induction was made using basiliximab and entanercept. Immunosuppressive therapy initiated with kidney transplantation with tacrolimus, mycophenolate mofetil and prednisone was also continued. The pancreatic islet transplantation consisted of an infusion of pancreatic islets suspended in a special liquid containing human albumin and heparin. Infusion of the islets was made through a catheter inserted through a percutaneous, transhepatic approach by the interventional radiologist to the main branch of the portal vein, under the control of ultrasonography and fluoroscopy. After the transplantation, islets started to function, which was confirmed by the presence of c-peptide in the blood. After an uncomplicated procedure, the patient was advised to take insulin in order to support the pancreatic islets struggling against excessive metabolic stimulation during engraftment into the liver tissue. Gradual reduction of daily insulin intake to about 10 units per day was achieved with significantly lower fluctuations of blood glucose concentration. On post-transplant day 75 after the procedure, in the mixed meal stimulation test performed without insulin (Boost 360 mL), adequate low levels of fasting glucose 116 mg/dL and 89 mg/dL after 90 minutes stimulation, with high levels of fasting and stimulated c-peptide (0,86 pmol/mL and 3.3 pmol/ml, respectively) were observed (Figure 1). Comparing the results of the same test carried

out on day 7 after the procedure, it confirmed the proper engraftment of the islets in the liver tissue and improvement in their function (Figure 1). Therefore, the patient was advised to stop using insulin. In the following months, A1c gradually decreased to reach 6.2 % in 6 months after transplantation. However, a month later, A1c increased to 7.6% and the same standardized mixed meal stimulation test showed worse glycemic control (fasting glucose 140 mg/dl) and slightly lower values of fasting and stimulated c-peptide comparing to day 75 results, what confirmed the continued presence of islets with reduced function (Figure 1). A blood test did not show the presence of anti-HLA antibodies that could indicate rejection. As the islets are scattered throughout the liver, a biopsy of this organ does not allow for diagnostic histopathology of islet graft.

Therefore, on June 12$^{th}$, 2015, the patient received a 2nd pancreatic islet transplant in the amount of 535,312 IEQ. The donor was a 28-year-old man who died due to cranial cerebral trauma with a compatible blood type 0 and with one match between HLA B antigen (5 incompatible antigens, no HLA antibodies were detected in the recipient in the solid-phase assays). This time, none of the HLA antigen incompatibilities found in previous transplants were repeated. The treatment with tacrolimus and mycophenolate mofetil was continued with a transient increase in the doses of both drugs. Prednisone was continued at a dose of 5 mg per day. In addition, basiliximab and etanercept were given. The procedure was carried out without complications. For the past two and a half years since the second islet transplantation, the patient does not take insulin, blood glucose values are normal, and A1c is within 6.0 - 6.2% range. Similarly, the function of the transplanted kidney is stable with a creatinine concentration of 1mg/dL. There is no proteinuria.

Progression of atherosclerosis of the lower limbs was observed, requiring the implantation of another stent in the left popliteal artery. Additionally, an ischemic ulcer was developed on the foot with no evidence of osteoarthritis. Retinopathy remained stable and did not require ophthalmological intervention. The quality of vision improved soon after the first islet transplantation as a result of better blood glucose control. The patient could significantly reduce the corrective effect of the glasses. Three years post-transplant, the patient did not have any new symptoms of coronary artery disease or neuropathy and did not require intervention or change in the dose of medication. The patient still has no anti-HLA antibodies in the blood, and there are no symptoms of rejection of the kidney or pancreatic islets. Antibodies to all three donors continue to be negative in the subsequent evaluations, although in 2 of 3 donors there was only one HLA antigen matched.

**Case 2.**

39-year-old male, with T1DM since age 20, with a history of stage 5 chronic kidney disease (CKD) due to diabetic nephropathy, with history of hypertension and recurrent herpes, received a kidney from a living donor (brother) on September 1st, 2012. Before the kidney transplantation he was on hemodialysis for 4 months through a permanent catheter implanted into his right venous angle. The blood type of the brother was compatible with the recipient's and the HLA compatibility comprised 1 matched antigen in A, B and DR groups (3 incompatible antigens). A four-drug combination of immunosuppression was used: glucocorticosteroids, tacrolimus (Prograf), mycophenolate mofetil (CellCept), with the induction of basiliximab. Immediately after the procedure, approximately 1500 ml of diuresis was observed with the reduction of plasma creatinine concentration. The patient did not require hemodialysis. The postoperative course was uncomplicated. Creatinine on discharge was 3.0 mg/dl, but within 2 weeks, it decreased to 1 mg/ml. The patient was diagnosed with chronic microangiopathic complications of diabetes and apart from nephropathy, neuropathy was also diagnosed. Due to proliferative retinopathy, patient was subjected to several courses of laser therapy. Diabetic macular edema of the left eye was treated with intravitreal injections of antibodies against endothelial growth factor. Coronary artery disease (CAD) and atherosclerosis of the intracerebral arteries and arteries of lower limbs, were excluded in tests performed as part of the evaluation for kidney transplantation. The patient’s weight was 85 kg with a BMI of 29.4 kg/m2.

One month before the initiation of hemodialysis, the patient started using an insulin pump integrated with the continuous glucose monitoring system. After changing the treatment regimen, A1c decreased from 11% to 6.3%. The daily insulin requirement was 70-90 units. However, despite this treatment, large fluctuations of glucose concentration were observed, and the patient complained of episodes of severe hypoglycemia 1-3 times per week. Also, there were hypoglycemic attacks, accompanied with confusion, signs of memory loss and visual disturbances. Therefore, at the beginning of 2013, just three months after a kidney transplantation, when the kidney graft function was stable with creatinine 1.0 mg/dl, the patient was offered a pancreas whole-organ transplantation or pancreatic islet transplantation. The patient chose pancreatic islet transplantation as a less invasive procedure, with a lower risk of complications. He was previously informed that compared to a whole-organ pancreas transplantation, the chance for complete insulin withdrawal is less and it may be necessary to perform subsequent islet infusions from different donors. On March 26th, 2013, pancreatic islets were transplanted in the amount of 625,054 IEQ isolated from pancreases procured from two deceased donors: a 28-year-old woman and a 47-year-old man, both died as a result of

intracranial hemorrhage and both had the same blood type 0 with the recipient. For both donors, all HLA antigens were incompatible. Recipient did not have anti-HLA antibodies. In the immunosuppressive treatment, tacrolimus, mycophenolate mofetil and prednisone were maintained. In addition, basiliximab and etanercept were given. The administration of thymoglobulin was skipped due to a concern of too excessive immunosuppression, as the patient had recurrent herpes in the past. Islets were infused through a percutaneous, transhepatic catheter introduced into the portal vein by an interventional radiologist, under the control of ultrasonography and fluoroscopy. After the transplantation, islets started to function, which was confirmed by the presence of c-peptide in the blood. As time progressed, insulin requirements decreased from 90 units to 20-30 units per day. The daily range in glucose level fluctuations decreased significantly from 30-300 mg/dl to 80-160 mg/dl, and A1c stabilized to less than 7%. From the patient's perspective, the most important improvement was quality of life coming with the complete elimination of severe hypoglycemia episodes. Constant fear against sudden death due to hypoglycemia and loss of consciousness attacks, paralyzed him and his family life. Additionally after islet transplantation, his dietary restrictions significantly decreased and he could eat pizza or hamburgers without constant blood glucose monitoring. Such a significant improvement in the quality of life associated with better glucose control due to the islet transplantation which resulted in the patient having no further interest for next islet infusion in order to completely eliminate need for insulin. Up to date, he had no symptoms of coronary artery disease, atherosclerosis of the carotid arteries and arteries in legs. He required further laser therapy due to retinopathy. Three years after the transplantation, the patient had a detectable c-peptide in the peripheral blood indicating islets function. The patient gained 10 kg of body weight, which in combination with the insulin resistance further induced by taking steroids, caused a greater need for insulin and an increase in A1c to 8%. Currently, the patient experiences drops in glucose concentration up to 60-70 mg/dl. However, due to islet transplantation and subsequent long-lasting good glucose control, the patient regained hypoglycemia awareness, and developed simultaneous symptoms of anxiety and sweating, which allowed the patient to react on time with proper meal. Currently, the patient is considering another islet transplant. The anti-HLA antibodies are still not detectable and the function of the transplanted kidney is stable with a creatinine of 1.2 mg/dl.

**Discussion**

Transplantation of the pancreas and pancreatic islets are currently the only method to restore the physiological secretion of endogenous insulin. Transplantation of pancreatic islets to the

liver via the portal vein is a safe method and is a minimally invasive alternative for the transplantation of the whole pancreas [1]. However, late metabolic outcomes after transplantation of the islets are not as good as in the case of a whole pancreas transplantation. Current technology allows isolation of 30-50% of islets from the donor's pancreas. Therefore, the recipient eventually receives significantly lower amounts of islets than what is present in a healthy organ. For this reason, even if the patient succeeds in complete discontinuation of insulin, the efficiency of β cells is borderline with reduced metabolic reserve. Obtaining insulin independence, although possible, especially with repeated infusions of islets from several donors, is not the main goal of pancreatic islet transplantation. The main goal, is to achieve a stable course of disease, minimize the risk of secondary complications and eliminate life-threatening episodes of severe hypoglycemia either with reduced insulin requirement or without insulin. This is because there is no guarantee for a long lasting effect of pancreatic islet transplantation. This is mainly due to the progressive loss of function of transplanted islets, even despite the excellent initial function of the graft. However, even in the case of only residual secretory function of the graft, patients still do not have severe, symptomatic hypoglycemia, and glycemic control is easier than without transplanted β cells. For this reason, the indications for islet transplantation, as a minimally invasive alternative to the whole organ transplant in patients with normal renal function are: type 1 diabetes with frequent and severe episodes of hypoglycemia, without prodromal symptoms and threshold of symptoms below 50 mg/dl of glucose concentration, with symptoms affecting central nervous system, i.e. impaired level of consciousness, confusion, seizures, sudden death (risk of lethal neuroglycopenia), progression of diabetes, despite modifications of insulin therapy, poor metabolic control and recurrent ketoacidosis [2]. Proper selection of patients for this procedure is important in terms of potential side effects of immunosuppressive medications which are introduced simultaneously with the islets transplantation. It has been shown that pancreatic islet transplantation has been associated with improved quality of life only in those patients, who before the procedure complained about the unawareness of hypoglycemia and the occurrence of hypoglycemic episodes made them dependent on the help of third parties. These patients were not able to predict, prevent and treat hypoglycemic attacks, which inevitably led to frustration, depression, job loss, fear of driving, and thus negatively affected quality of daily living and performing their roles in the family. In patients, in whom the unsteady course of diabetes did not affect daily functioning, no benefits were gained in improving the quality of life [3]. Therefore, just like in the case of other procedures, the key to a successful qualification for pancreatic islet transplantation seems to be realistic expectation from both the patient and the physician. If the patient already

received the kidney graft or another organ and has already been on immunosuppressive therapy, the indication for the transplantation of the islets can be expanded, as the islet infusion is a minimally invasive procedure with a low risk of complications. In 10% of patients, hepatic hemorrhage may occur, which most often requires only blood transfusion and only 1% of patients need surgery. Portal vein thrombosis is a rare complication, observed in about 3% of cases, usually partial, affecting the small branches of the portal vein and usually resolves after anticoagulation therapy without any clinical consequences. In the majority of patients with type 1 diabetes requiring kidney transplantation, inappropriate glycemic control has been chronically observed. After kidney transplantation, glycemic control usually worsens as a result of taking steroids and calcineurin inhibitors. Therefore, islets after kidney transplantation can bring significant benefit for patients in terms of better glycemic control expressed by lowering A1c and may stop or limit the progression of diabetic complications, including hypoglycemic attacks, atherosclerosis, retinopathy, neuropathy, as well as diabetic nephropathy in a transplanted kidney. This is confirmed by cases described above. In both cases, pancreatic islet transplantation was done after the failure of initially proposed methods of treatment, i.e. insulin pump with continuous glucose monitoring and pancreas transplantation (Case 1). Islet infusion into the liver through the portal vein was not associated with complications. Permanent insulin independence was not obtained after a single islet infusion. Even with losing some of the islet function, both patients had a significant benefit in terms of eliminating life affecting hypoglycemic episodes. The metabolic control measured by the A1c concentration also improved significantly. Patients had stabilization of their retinopathic and neuropathic disease. The function of the kidney transplanted in both patients remained stable, without signs of proteinuria. Since no protocol biopsy was performed, it was not possible to assess development of diabetic nephropathy changes in the transplanted kidney. Although the diabetic nephropathy may lead to end-stage failure of the allograft after several years, when acting together with other factors it may further shorten the time to end stage renal failure of the transplanted kidney [4, 5].
Insulin independence was obtained only in the patient who received two subsequent infusions of pancreatic islets (Case 1). It is convergent with previously published results, that patients who received two subsequent islet infusions compared with a single infusion were insulin independent more often and for a longer period of time, and had a better function of the transplanted islets evaluated by c-peptide and A1c concentration [6, 7]. Similar results were obtained in another group of islet after kidney recipients in 7 year follow-up [8]. It is worth to mention that the deterioration and ultimately loss of transplanted β-cell function was correlated with the increase in body weight. It seems that similarly as in type 2 diabetes, in case of an

increase in insulin resistance, compensatory hyperinsulinemia leads to exhaustion of the secretory capacity of transplanted β cells.

It is important to stress that in subsequent transplantations (kidney transplantation >> pancreatic islet transplantation >> second pancreatic islet transplantation), despite the exposure to numerous non-compliant HLA antigens, no production of anti-HLA antibodies and increasing PRA rate was observed. Also no deterioration of kidney function due to immunization and rejection was observed. The reason is proper administration of immunosuppressive drugs, constant maintenance of the appropriate level of these drugs, which protects against immunization and rejection [9]. When pancreatic islet transplantation was performed in patients with normal renal function (without renal transplantation), the loss of islet function was associated with immunization of the recipient due to discontinuation of immunosuppression leading to development of anti-HLA antibodies [10]. In addition, in these patients the toxicity of tacrolimus led to deterioration of renal function over time, but to a lesser extent than in the control group of patients who despite optimized insulin treatment had uncontrolled diabetes awaiting islet transplantation [11]. Therefore, kidney recipients who already take immunosuppressive medications to prevent rejection of a transplanted organ are a group of patients that can greatly benefit from β-cell transplantation with the acceptable risk of side effects.

**Summary**

Transplantation of pancreatic islets is an alternative and complementary method for the transplantation of the whole pancreas. As a minimally invasive procedure, it is a safe method of treatment with a low risk of complications. It seems to be the optimal form of treatment especially for patients after kidney transplantation, already receiving immunosuppression to prevent rejection of transplanted kidney, especially when additional risk coming with the procedure is minimal. In addition, the function of the transplanted kidney remains stable and there is no increase in the percentage of PRA observed, what otherwise may make it difficult to find a donor in the future if subsequent kidney transplantation needed. Transplantation of pancreatic islets allows the patient to achieve a stable course of diabetes, minimize the risk of secondary complications and eliminate life-threatening episodes of severe hypoglycemia. Due to the progressive loss of function of transplanted islets and time limited insulin independence, even despite the good initial function of transplanted β-cells, the achievement of insulin independence should not be the primary goal of pancreatic islet transplantation. The patient must participate in the decision-making process and be familiar with the real benefits and risks

involved in the procedure. Presented case reports refer to patients undergoing pancreatic islet transplantation and remain under the care of Dr. Piotr Witkowski's Team from the Department of Surgery, Transplant Division at the University of Chicago.

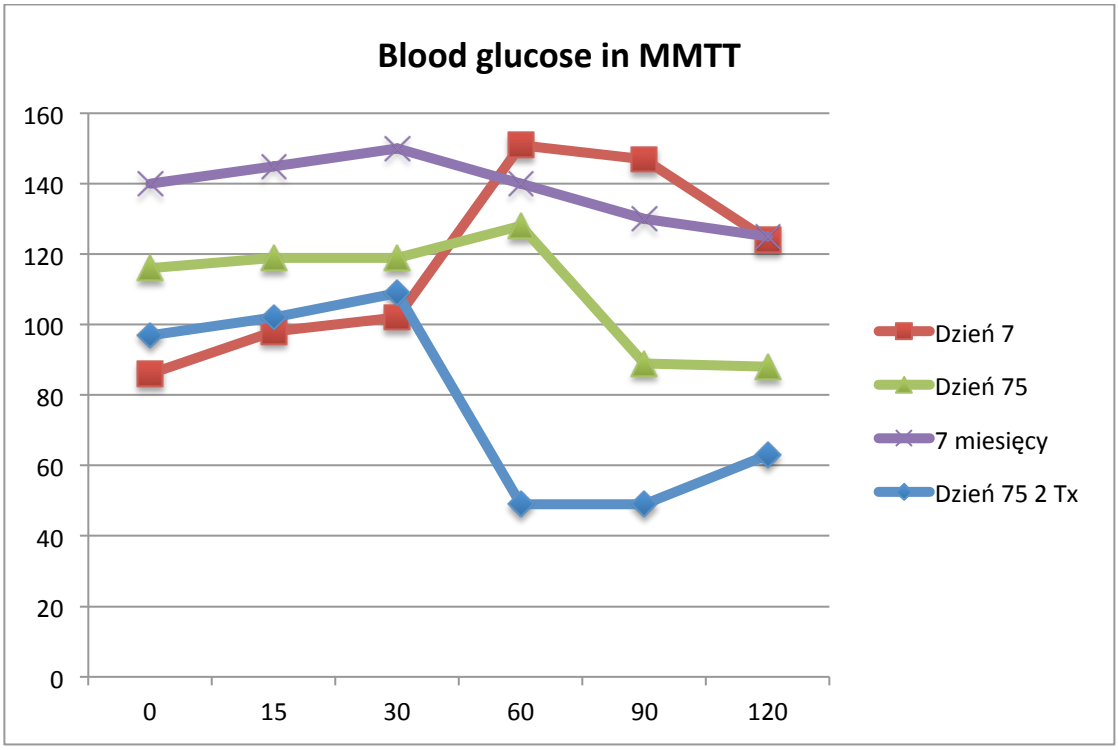
**References**


1. Gerber PA, Pavlicek V, Demartines N. Simultaneous islet-kidney vs pancreas-kidney transplantation in type 1 diabetes mellitus: a 5 year single centre follow-up. Diabetologia. 2008; 51: 110-9.
2. Pedersen-Bjergaard U, Pramming S, Heller SR i wsp. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev. 2004; 20: 479-86.
3. Benhamou PY, Milliat-Guittard L, Wojtusciszyn A i wsp. Quality of life after islet transplantation: data from the GRAGIL 1 and 2 trials. Diabet Med. 2009; 26: 617-21.
4. Nyumura I, Honda K, Babazono T i wsp. Recurrence of diabetic kidney disease in a type 1 diabetic patient after kidney transplantation. Nephrology (Carlton). 2015; 20 Suppl 2:90-2.
5. Salifu MO, Nicastri AD, Markell MS i wsp. Allograft diabetic nephropathy may progress to end-stage renal disease. Pediatr Transplant. 2004; 8: 351-6.
6. Borot S, Niclauss N, Wojtusciszyn A i wsp. Impact of the number of infusions on 2-year results of islet-after-kidney transplantation in the GRAGIL network. Transplantation. 2011; 92: 1031-8.
7. Cure P, Pileggi A, Froud T i wsp. Improved metabolic control and quality of life in seven patients with type 1 diabetes following islet after kidney transplantation. Transplantation. 2008; 85: 801-12.
8. Gerber PA, Locher R, Zuellig RA i wsp. Glycemia, Hypoglycemia, and Costs of Simultaneous Islet-Kidney or Islet After Kidney Transplantation Versus Intensive Insulin Therapy and Waiting List for Islet Transplantation. Transplantation. 2015; 99: 2174-80.
9. Tufveson G. An experience of pancreas and islet transplantation in patients with end stage renal failure due to diabetes type I. Curr Opin Organ Transplant. 2009; 14: 95-102.

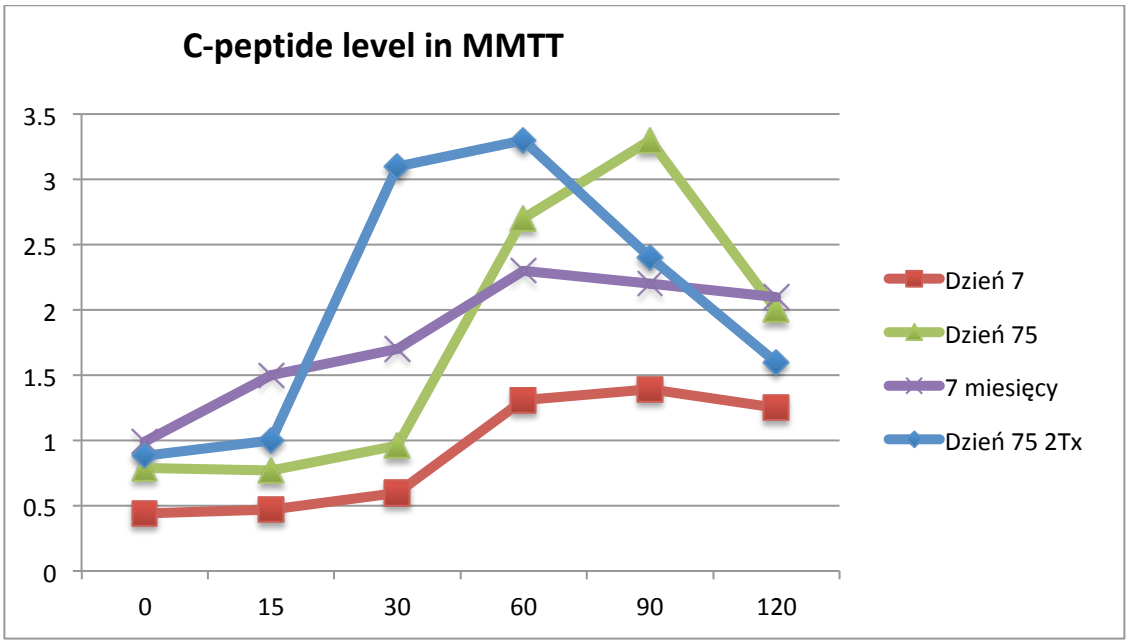
10. Campbell PM, Senior PA, Salam A i wsp. High risk of sensitization after failed islet transplantation. Am J Transplant 2007; 7:2311–2317.
11. Warnock GL, Thompson DM, Meloche RM i wsp. A multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. Transplantation. 2008; 86: 1762-6.

Figure 1

A


Blood glucose in MMTT
160
140
120
100
80
60
40
20
0
0
15
30
60
90
120
Dzień 7
Dzień 75
7 miesięcy
Dzień 75 2 Tx

B


C-peptide level in MMTT
3.5
3
2.5
2
1.5
1
0.5
0
0
15
30
60
90
120
Dzień 7
Dzień 75
7 miesięcy
Dzień 75 2Tx