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REVIEW

INSULIN REPLACEMENT THERAPY IN PATIENTS WITH TYPE 1 DIABETES BY ISOLATED PANCREATIC ISLET TRANSPLANTATION

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Abstract: Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia which causes micro- and macrovascular complications. A significant increase in diabetes morbidity rate has been observed. It is estimated that in year 2030 there will be 552 million diabetics worldwide. Type 1 diabetes requires lifelong treatment with insulin. The only available treatment of diabetes restoring physiological glucose metabolism is transplantation of pancreatic β cells in form of pancreas or isolated pancreatic islets transplantation. The treatment restores normoglycemia and reduces chances of complications of diabetes. Over the past 10 years there has been significant progress in the development of the islet transplantation procedure. Constant improvement of the method, in particular the development of islets isolation and sourcing techniques, shows promise. According to the Collaborative Islet Transplant Registry in 1999-2009, there have been performed 1,072 allotransplantations. This paper summarizes the indications and contraindications for the procedure, the transplantation process, as well as the surgical procedure and immunosuppressive treatment. The review presents problems related to pancreatic islet cells transplantation and standard scheme of immunosuppressive treatment, requiring a solution.

Keywords: diabetes, isolated islets, islet transplantation

Definition and classification of diabetes mellitus

Diabetes is classified as a metabolic disease, characterized by hyperglycemia caused by insulin secretion defects and leads to microvascular damage, dysfunction or organ failure (1, 2).

According to the World Health Organization diabetes classification includes type 1 diabetes, type 2 diabetes, other specific types of diabetes and gestational diabetes (2-4).

Causes of the so-called secondary diabetes are exocrine pancreas disorders: pancreatitis, pancreatic trauma, and pancreatectomy, pancreatic cancer, cystic fibrosis of pancreas, hemochromatosis and fibrocalculous pancreatopathy (5).

Morbidity and mortality rate of diabetes

The dramatic increase in diabetes prevalence worldwide has the characteristics of an epidemic. It is estimated that the number of people with diabetes in the world in 2011 was 366 million, which represents about 6% of the population and in 2030 will exceed 552 million. The International Diabetes Federation estimates that in 2011 in Poland there were more than 3 057 000 diabetics. In 2030 the number of patients will grow to over 3 409 000. Diabetes should be considered one of the main threats to the health of the world population , posing a great socioeconomic problem (6-8).

Despite continuous progress in diagnosis and treatment of diabetes being made, the disease is an important cause of cardiovascular diseases, chronic kidney failure, blindness or lower limb amputation (5, 9, 10). It has caused 4.6 million deaths in 2011 (6).

For many years there have been continued efforts to achieve normoglycemia in diabetic

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patients (11). The effective method of pancreatic islets isolation had been worked on for decades, with Stanislaw Moskalewski, professor of the Medical University of Warsaw as its pioneer, who in 1965, successfully isolated pancreas islets from a guinea pig (11, 12). This method has been modified in 1967 by Lacy and Kostianovsky (13, 14). In 1972, Ballinger and Lacy proved in animal studies that transplants of pancreatic islets lead to a state of normoglycemia (15). Ricordi conducted a new, automated method for isolation of human pancreatic islets in 1988 (11, 12) and the first human transplant has been performed in 1974 (16).

According to the Collaborative Islet Transplant Registry (CITR) in the period of 1999-2009 took place more than 1072 allotransplants of pancreatic islets, the annual independence from insulin therapy achieved 65% of patients (17).

Significant progress on pancreatic islets transplantation has been made in 2000, when Shapiro et al. achieved a state of persistent normoglycemia in pancreatic islet transplantation patients, (Edmonton Protocol). Innovations have been introduced: the use of a greater amount of pancreatic islets taken from at least two donors, corticosteroid-free therapy, administration of a combination of sirolimus, tacrolimus and monoclonal antibodies against the interleukin-2 receptor. After applying these procedures exogenous insulin independence has been achieved in all patients (11, 18).

In 2008, the two first isolated pancreatic islet transplantations have been performed successfully in Poland at the Medical University in Warsaw (19).

Methods of diabetes treatment

The discovery of insulin and anti-diabetic oral drugs, have contributed to a longer average lifespan in diabetes patients, however, it did not provide insulin at physiological concentration and complete recovery. The use of both human insulin, as well as its analogues, involves a lot of side effects, particularly the risk of hypoglycemia (5, 20). It has been observed that cancer mortality in patients with diabetes, especially with type 2 diabetes, is higher, including pancreatic, colorectal and breast cancer (21).

Type 1 diabetes requires lifelong insulin therapy. The only available treatment of diabetes restoring physiological glucose metabolism is pancreatic β cells transplantation, in form of pancreas or isolated pancreatic islets transplants (22). This method of treatment normalizes glycemia and effectively limits development of complications and improves life quality (23). Recently, great expectations are connected with the use of new insulin pumps and continuous glucose monitoring (24, 25).

Complete pancreas transplantation is still more often performed than isolated islets transplantation. The recipients of both methods are similar regarding age, gender, body weight and duration of diabetes. Differently than in case of pancreas transplants, in order to collect the islets it is recommended to have overweight or older donors can be used, so both methods of treatment do not compete with each other. Islet transplantation is a less invasive method with less serious complications. Both methods are comparable in scope of safety (26, 27).

In the future, potential sources of large mass pancreatic β cells, would be insulin producing cells (IPCs) in the form of e.g., embryonic, adult, mesenchymal and hematopoietic stem cells. Thanks to this method, the problem of lack of donors may be solved and the goal of insulin independence could be achieved (28, 29).

Isolated pancreatic islets transplantations in the world

The Collaborative Islet Transplant Registry is the largest pancreatic islets transplant registry, taking into account data from the majority of centers in the United States of America and Canada and several centers in Europe and Australia. In its latest annual report of 2010, results have been published for 1,072 treatments with pancreas allotransplants from 1,187 donors, performed in years 1999-2009 in 32 centers (27 American, 3 European and 2 Australian). The research has been conducted among 571 recipients, on 481 cases (897 infusions) of only pancreatic islets transplants, and in 90 (175 infusions) recipients of kidney transplants. Thirty one percent of the recipients received a single islet infusion, 47% received two, 20% received three and 2% received 4-6 infusions. In 65% of the cases insulin independence lasted for over a year. That increased to 75% after two years (17).

In the period of 1999-2004, 65 cases of human islets transplants and a total of 128 infusions have been performed at the University of Alberta in Edmonton. One year after transplant, total independence from exogenous insulin has been maintained in about 70% of patients, two years later in only 40%, three years later - 22%, four years later - 17%, and five years after the transplant in less than 10%. The mean duration of insulin independence has been 15 months. C-peptide has been present in 80% of patients 5 years after the transplant, but they required the use of exogenous insulin (30).

No detailed central record of the islet transplants is being kept in Europe, for that reason only

fragmentary data are available. According to the Eurotransplant International Foundation, an association of organizations in Austria, Belgium, Croatia, Germany, Luxembourg, the Netherlands and Slovenia, in 2007-2011, 89 transplants have been performed on 54 recipients , with 207 donors (31). In comparison, in the years 1966-2010, more than 37,000 pancreas transplants have been performed (over 25 000 of which - in the United States) including 75% of simultaneous kidney and pancreas transplants, 18% transplantations of pancreas after kidney, and 7% of pancreas alone (32)

Pancreatic islets transplantation

Indications

Indications for recipient selection are: duration of diabetes = 5 years, negative stimulated C-peptide, intensive diabetes management, at least one severe hypoglycemic event. Detailed criteria of patient selection are described in *Organ Transplantation* by Kaufman and Hering (33, 34).

Indications for autotransplantation of isolated islets are: treatment of resistant pain in chronic pancreatitis or cachexia caused by long starvation. Contraindications for an autotransplant are pancreatic cancer or an infection (35).

Contraindications

Exclusion criteria for islet recipients selection include contraindications to immunosuppression. Absolute and relative contraindications are described in *Organ Transplantation* by Kaufman and Hering e.g., diabetes lasting less than 10 years, insulin requirement of > 0.7 IU/kg/day, positive C-peptide response, HbA1c > 10%, incorrect results of urine tests, pregnancy, active infection, liver dysfunction in present or in history and severe cardiovascular disorders (13, 33-35).

Surgical procedure and isolation of pancreatic islets

There are five types of isolated pancreatic islet transplantation: autotransplantation in patients after pancreatectomy, allotransplantation in patients after total pancreatomy, allotransplantation in patients with type 1 diabetes, fetal allotransplantation or xenotransplantation in type 1 diabetes, allotransplantation of islets in type 2 diabetes (36).

The pancreas is taken from brain-dead multiorgan donors, but the successful transplants of islets have been noted from donors after cardiac death. The selection of donors is strict and includes e.g., age, cold and warm ischemia times, body mass index, cause of death, serum amylase or lipase levels, glycemia, incidence of hypertension, alcoholism or smoking. In order to achieve normoglycemia most recipients are required to undergo 2-3 infusions. It is estimated that to achieve full insulin independence up to 10,000 (5,000-10,000) islets equivalents per kilogram are necessary. It is impossible to get that amount from a single donor (35, 37-40).

In general, islet transplants are low-invasive and safe. An important requirement in islet grafts is the cold ischemia time, which should not be shorter than 2 h or longer than 12 h, and appropriate surgical technique in order to remove the whole pancreas en block with the duodenum and spleen, causing no damage to the organ capsule or duodenal wall has to be applied. The anatomical anomalies and incidence of cancer are possible serious problems. After removal and surgery, the pancreas and the exocrine organ tissue is digested by injection of the pancreatic duct with a cold solution of collagenase or liberase (35, 41).

During the complicated, multistage procedure islets are placed in a Ricordi digestion chamber with the sieve for islets, a solution of enzymes flows through it. The aim of this procedure is to select the insulin secreting part of the pancreas. The digestion process is monitored by assessment of quantity, viability, function and sterility of the islets. Currently, a two-layer cold-storage method is in use, in which the pancreas is immersed in the UW (University of Wisconsin) solution and PFC (perfluorochemical) solution. This enables adequate perfusion and cooling of pancreas. Digested islets are isolated by centrifugation in density gradient and purified islets are cultured (33, 35, 42-45).

During autologous transplantation the most suspicious fragment of pancreas must be taken for the histopathological examination to preclude possibility of cancer (35).

There are two operating methods: laparotomy with cannulation to the mesenteric vein (portal vein flow) and radiological, subcutaneous access to portal vasculature using fluoroscopy and ultrasonography. The islets are suspended in 200 mL of medium containing heparin (70 units/kg) are then, slowly injected into the portal vein under local anesthesia (33, 35).

Post-transplant aim is to maintain blood glucose levels at 80-120 mg/dL. It is recommended for outpatients to perform multiple daily glucose measurements (five times a day) and the use of multiple insulin injections or continuation of insulin in the case of persistent hyperglycemia. Heparin should be administered for 2-10 days post-transplant. Antimicrobial prophylaxis is applied pre-transplant (44, 46).

During islet preparation, the system of capillaries supplying the pancreas is destroyed, however, a method to estimate the structure of the graft and the degree of damage have not been developed so far. The only indirect way is to monitor the ability to secrete insulin. To monitor graft function it is recommended to determine C-peptide level, which concentration should be above 0.3 ng/mL, the level of glycosylated hemoglobin (HbA1c) and blood glucose. The optimum indicator for assessment of early graft failure is an intravenous glucose tolerance test and mixed meal tolerance test, but so far there is no early, specific marker of pancreatic islet graft rejection and autoimmune response. It should be noted that glucose control can be used as a graft rejection indicator, as the variability of blood glucose helps to identify graft dysfunction (35, 47-50).

Complications

Complications may occur after transplantation of isolated pancreatic islets, such as elevated liver enzymes, abdominal pain, nausea/vomiting, fatty liver, peritoneal hemorrhage, portal vein thrombosis, bleeding and gallbladder puncture. There are also adverse effects associated with immunosuppressive therapy. Currently, due to constant improvement of pancreatic islet suspension preparation techniques, clinical risk of thrombosis within the portal system has been significantly reduced. Estimated cost of the isolated islet transplantation procedure and patient treatment in the first year is, depending on the center, almost 80,000 euro. A quarter of this sum is related to the treatment of adverse events (30, 33, 51-56).

Immunosuppression

Islet transplantation allows diabetics to achieve good glycemic control and full insulin independence and prevent prevalence of diabetic complications, however, it requires the lifelong use of immunosuppression. Immunosuppression reduces the risk of transplant rejection and restricts autoimmune destruction of pancreatic islets. Usually, insulin use is replaced by a chronic immunosuppressive therapy, which is fully justified in patients with poor metabolic control or already receiving immunosuppressants because of another graft (57, 58).

Initially, immunosuppression regimens include azathioprine, cyclosporine, corticosteroids, and allowed maintenance of insulin independence after one year in only about 10% of people. The introduction of a new, less diabetogenic treatment algorithm (the so-called Edmonton Protocol) has contributed to the achievement of complete insulin independence in more than 80% of patients, due to reduction of drug toxicity to β cells and avoidance of peripheral insulin resistance promoting drugs. Currently recommended are simulect (anti-CD25 antibody given pretransplant and posttranplant), sirolimus and tacrolimus in small doses. Instead of tacrolimus, cyclosporine, mycophenolate mofetil and some experience with FTY 720 are introduced to the clinical use (18, 45, 58-60).

Immunosuppressants increase risk of certain cancers, especially in highly immunized recipients. During immunosuppressive therapy, cancers are more common. It has been shown that immunosuppressive drugs limit the cell's DNA repair mechanisms and inhibit apoptosis (61-63).

One of the most common cancers following islet transplantation is the hepatocellular carcinoma, also associated with increased incidence of liver cirrhosis, HCV and HBV infection, alcohol abuse, the impact of mycotoxins and sex hormones. Important in the pathogenesis of this disease are morphological and physiological changes in liver cells and changes in insulin dependent signal paths. Adverse effect of carcinogenesis is a combination of both hyperglycemia and hyperinsulinemia associated with a limited number of β cells after pancreatic islet transplantation (64-66).

During sirolimus and tacrolimus therapy, in more than 70% of cases ovarian cysts were detected in premenopausal women after isolated pancreatic islet transplantation. It is assumed that sirolimus prevents physiological rupture of the follicular wall during ovulation, which causes ovarian cysts (67).

Further observations of individuals administered chronic immunosuppressive drugs after islet transplantation are necessary. So far, there are no population-based studies suggesting specific biomarkers associated with carcinogenesis in transplant patients (61).

Other clinical issues

With isolated pancreatic islet transplantation procedure not only immunosuppression-related complications are involved, but also problems with a limited number of donors, selection of suitable donors, islet isolation procedures and small amount of isolated islets (68).

Due to the increasing demand for organs and requirement of up to 10,000 islets/kg equivalent (the pancreas usually weighs about 50 grams (1 million islets), 2-3 donors), the number of pancreas donors is insufficient. Research on use of donors after cardiac death are promising. (33, 35, 36, 39).

It is proved that about 50-70% of pancreatic islets implanted into the liver are destroyed (inflammatory response and apoptosis). The process of isolation causes apoptosis. After implantation, the islet structure is destroyed. As a result of that, the islets lose their function and die. The important factor is hypoxia which lasts until revascularization (33, 69, 70).

Oxidative stress is also a significant factor leading to partial loss of islets. Too low antioxidants content (catalase, dysmutase and glutathione peroxidase) in pancreatic cells makes them more vulnerable to effects of free radicals, which contributes to the regulation of pro-inflammatory cytokines, chemokines and adhesion molecules, leading to destruction of pancreatic cells (71, 72).

Cytokines activated in the donor after brain death (such as TNF-α, IL-1β, IL-6) also accelerate the death of islet cells. Brain death results in increased levels of tissue factor (TF) and monocyte chemoattractant protein (MCP-1), which are the main factors causing instant blood-mediated inflammatory reaction (IBMIR) – the death cause of large number of pancreatic islets shortly after transplantation (73, 74).

Transplantation site

Intrahepatic islet transplantation involves the maintenance of insulin release to the liver, which provides physiological portal delivery of insulin and a tight glycemic control. However, the possibility of thrombosis or hemorrhage restricts use of portal site. The production of nitric oxide, damaging the transplanted cells, leads to graft dysfunction. Low oxygen concentration in the portal vein is another factor causing graft damage. During preparation of islets the negative morphological changes appear and damage function of, especially small, islets. Loss of β cells in early stage of transplantation due to apoptosis is associated with removal of growth factors (33, 75-78).

One of the main research strategies is the search for a new, alternative pancreatic islet graft sources. From a clinical point of view, the optimal location for an islet transplant should provide proper islet vascularization and hormones (secreted by the islets) drain to the liver in a short time. A place for pancreatic islet transplantation should be easily accessible for both islet transplanting and their removal. Currently, liver is considered best for islet graft. In experimental conditions islets have been transplanted subcutaneously, intramuscular, to kidney, bone, testicles, brain, thymus, peritoneal cavity, omentum, spleen, pancreas, intestinal wall and stomach (68, 75, 79).

Islet transplantation under the kidney capsule is a very invasive surgery and does not provide adequate oxygen supply. The procedure requires a large cell mass. In the spleen, islets are exposed to lymphocytes and there is a higher risk of hemorrhage. Transplantation of islets to the circulatory system is not a promising method because there is a high risk of instant blood-mediated inflammatory reaction and thrombosis, and also graft is difficult to follow-up. Transplant to the patient's own pancreas in type 1 diabetes is marred by the effects of autoimmune reaction. Intraperitoneally and in omentum isolated pancreatic islets have a short live-span and the treatment requires a large mass of cells (75).

Analysis of results from 2008, identifies the stomach as a potential isolated pancreatic islet transplant location. First positive results of islet transplantation into the gastric submucosa have been observed by Champault et al. in 1978. Sageshima's et al. research confirmed that the small bowel subserosal space could be considered as an alternative location for a graft. Also following studies describe gastric submucosa as a potentially beneficial graft site, with the advantage of rich vascularization. In April 2009, results of research with experimental animals at the Medical University of Warsaw have been published, which confirmed that gastric mucosa may be an optional place for isolated islet transplantation in pigs. A later report by Echeverri et al. (86) showed that the endoscopic gastric submucosa islet transplantation method is safe, minimally invasive, and producing good results in terms of graft survival and function (75, 80-86).

On the contrary, in 2008, Rafael E. et al. (87) published the results of a two-year observation of a seven year old child with congenital, severe acute pancreatitis, after islet auto-transplant administered intramuscularly to the brachioradialis muscle. The treatment helped significantly to reduce the child's need for exogenous insulin and to get a quick response to changes throughout the day of insulin needs. This results indicate that muscle tissue may be an alternative site for transplantation of isolated pancreatic islets, however, a disadvantage of this procedure is the low level of angiogenesis, although studies in animals have shown that by using bioengineering neovascularization and graft survival can be enhanced (87-89).

The recent study has shown that an isolated venous sac prepared from the lumbar artery can be a favorable transplantation site, which assures engraftment and taking on of pancreatic islets function (90).

Clinical outcomes

It has been shown that successful transplantation of isolated pancreatic islets allows to achieve normalization of blood glucose and temporary permits to obtain full insulin independence (91, 92).

According to results of the British Columbia Islet Transplant Program, transplantation of isolated pancreatic islets is associated with reduced risk of development and progression of microvascular complications of diabetes: nephropathy, neuropathy and retinopathy in comparison to intensive medical treatment. Also, the improvement of HbA1c level is better in patients after transplantation (93-95).

In the follow-up (University of Alberta and University of British Columbia) improvements in metabolic control of diabetes have been noticed and the risk of severe hypoglycemia events have been reduced (96, 97).

The last Collaborative Islet Transplant Registry have shown improvement of islet transplantation outcomes since 2007. The procedure becomes more effective and there are less adverse effects observed (17, 98).

CONCLUSIONS

Over the past 10 years there significant progress has been made in the development of the islet transplantation procedure. The change of the immunosuppressive protocol in 2000 allowed introduction of this method for clinical practice for diabetes treatment.

The treatment has been recommended for curing diabetes in the population of patients with poorly controlled glycemia or frequent episodes of severe hypoglycemia.

The method is extremely promising. Its benefits in good glycemic control, less frequent hypoglycemic events and reduction of progression of microvascular complications.

Undoubtedly, existing methods will require further modification. Many problems still require solutions e.g., lack of donors, adverse effects in relation to implanting islets to the portal vein and death of islets during their preparation.

In conclusion, the β cell replacement therapy is one of alternative and effective, as well as a safe method of treatment for patients with diabetes mellitus type 1.

This method of treatment provides long term normoglycemia, which was documented by clinical outcomes. It should be emphasized that although whole pancreas transplantation provides long-term insulin independence, a major advantage of transplant of isolated islets of the pancreas results in a minimal morbidity and mortality rates, as well as lack of risk of high level of immunosuppressant, which might be an important factor in occurrence of infections.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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