DOI: 10.15825/1995-1191-2020-1-184-195

TRANSPLANTATION TECHNOLOGIES FOR TREATMENT OF CARBOHYDRATE METABOLISM DISORDERS

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The review includes results of retrospective and prospective clinical studies (foreign and national) and guidelines on the use of transplantation technologies for treatment of type 1 diabetes and pancreatogenic diabetes in chronic pancreatitis and pancreatic conditions. Modern data on prevalence of diabetes and modern insulin delivery methods are presented. Results of transplantation of pancreas and islets of Langerhans in primary insulin-dependent conditions are considered. Analysis of the technology for isolation and autotransplantation of islets after pancreatectomy in chronic pancreatitis and benign tumor diseases are given.

Keywords: pancreas, type 1 diabetes, pancreatogenic diabetes, pancreas transplantation, islets of Langerhans.

INTRODUCTION

Pancreatic conditions are associated with type 1 diabetes (T1D) and pancreatogenic diabetes mellitus (PD). T1D is characterized by autoimmune destruction of insulin-secreting cells resulting in absolute insulin deficiency. This disease is a significant medical and social problem for several reasons. Cases of T1D are rising every year. In Russia, 3.12% of the population (4,584,575 million people) were diabetic as of January 1, 2019. About 256,200 of these had T1DM. Currently, the average prevalence of T1D in Russia is 174.4 per 100,000 population. In 2018, a total of 10,805 new T1D cases were detected [1]. The vast majority of patients are children and young people under the age of 30. Carbohydrate metabolism disorders over time lead to acute fatal or chronic disabling diabetes complications [2]. Estimates from the Federal Diabetes Registry show that in T1D, 33.6% of patients developed diabetic polyneuropathy, 27.2% – diabetic retinopathy, 20.1% – nephropathy, 12.1% – diabetic macroangiopathy, 4.3% – diabetic foot syndrome, 3.5% – coronary heart disease, 1.5% – cerebrovascular disease, and 1.1% had myocardial infarction. Indicators presented are determined by the data on number of patients that visited the hospital. With active screening, incidence of such complications will certainly increase [3]. T1D patients have limited adaptability and self-actualization. Treatment requires huge expenses on expensive drugs and self-monitoring devices. Optimistic analysis based on the Russian sample showed that the average annual cost per patient with T1D was 81,100 roubles. The cost of treating patients with existing chronic complications and not reaching the target levels of glycated hemoglobin is much higher than in patients without complications with compensated diabetes [4]. There is no doubt that preventing or slowing down the progression of diabetes complications can be achieved through adequate long-term control of glycemia levels. Lifelong insulin therapy remains the only treatment available. Despite the emergence of pharmacokinetically more adapted insulin drugs, individual self-monitoring blood glucose devices (glucometer and continuous real-time monitoring systems) and insulin injection devices (insulin syringes and insulin pumps), stable glycemic parameters are not always achieved. Fluctuations in blood glucose levels, episodes of hyperglycemia and hypoglycemia are observed in almost all patients. This is due to differences in insulin requirements depending on diet, physical activity and many other factors that are difficult to foresee or control. Creation of a closed loop "artificial pancreas" based on inverse correlation between current blood glucose levels and the insulin dose administered is only in the clinical trials phase.

Pancreatogenic diabetes (PD) is a consequence of the loss of pancreatic parenchyma resulting from chronic relapsing pancreatitis, pancreatic necrosis, and partial or total pancreatectomy. This review focuses on patients who have undergone pancreatectomy for painful chronic relapsing pancreatitis or benign pancreatic tumors. Unlike T1D, which selectively destroys beta cells, PD is characterized by a lack of not only insulin, but also other islet hormones regulating glucose metabolism rates. Despite rare development of ketoacidosis and moderate hyperglycemia, these patients are prone to brittle diabetes with high variability of glycemia and repeated

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severe hypoglycemia, which reduces their recognition. Incidence of chronic micro- and macrovascular complications in T1D and PD is the same.

The use of transplantation technologies may be a promising option for replacing lost insulin-producing function. Achieving a euglycemic state will allow patients with pancreatic conditions to avoid the negative impact of hyperglycemia – the trigger mechanism for complications – and, most importantly, reduce the likelihood of developing severe, sometimes fatal, hypoglycemic conditions [5].

ANATOMICAL AND PHYSIOLOGICAL RATIONALE FOR THE USE OF TRANSPLANT TECHNOLOGIES

The human pancreas is a glandular organ that includes the exocrine and endocrine parts.

The exocrine part of the pancreas is represented by pancreatic acini and the excretory duct system.

The endocrine part of the pancreas is formed by pancreatic islets lying between the acini (islets of Langerhans). Islets of Langerhans contain 20–25% glucagon-producing alpha cells and 75–80% insulin-producing beta cells, somatostatin-producing D cells, VIP (vasoactive intestinal polypeptide) cells and PP (pancreatic polypeptide) cells. With age, there is a change in the pancreas between its exocrine and endocrine parts – the endocrine component (number of islets) reduces.

The pancreas has about 10,000,000 islets, which are compact clusters of secretory cells arranged in bunches or cords. Cells surround the capillaries of the islets in layers, being in close contact with the vessels.

TRANSPLANTATION TECHNOLOGIES

1. Pancreas transplantation

Transplantation of beta cells as part of an organ or isolated as a cell suspension is a pathogenetically justified method of T1D treatment. Despite many animal experiments, the first successful pancreas transplant was performed simultaneously with a renal graft to treat a T1D patient in 1966, at the University of Minnesota, and was conducted by William Kelly and Richard Lillehei. Until 1980, the operation was considered experimental. Active interest in pancreas transplantation returned in the late 1970s amid improved immunosuppressive therapy and surgical techniques [6].

In Russia, simultaneous kidney-pancreas transplantation with grafts obtained from a deceased donor was first performed by Valery Shumakov in 1987 [7]. Successful transplantation of a gland fragment from a living related donor was performed by Sergey Gauthier [8].

There are 44 transplant centers in Russia, but only four of them perform pancreas transplantation. In 2018, 17 pancreas transplants were performed [9].

Important factors for successful functioning of a pancreatic graft include recipient selection, assessment of the donor and the donated organ. Primary selection is based on blood group compatibility and a negative cross-match response. The number of HLA matches is important for long-term graft functioning [10].

Based on the outcome of 445 transplant surgeries, A. Gruessner et al. showed that donors older than 45 years and obese donors are a significant factor for such complications as major vessel thrombosis, intra-abdominal infection, and failed pancreatodigestive anastomotic failure [11]. Similar data are demonstrated by domestic authors [12].

Absolute contraindications for pancreas transplantation include functional disorders of the cardiovascular system, such as low cardiac output fraction, unstable coronary heart disease, mental diseases, noncompliance, active infection, and malignant tumor [13].

Diabetic nephropathy is the main criterion determining the transplantation option to choose (isolated or simultaneous). Less than 40 mL/min reduction in creatinine clearance, or dysfunction in the previous renal graft is an indication for simultaneous kidney-pancreas transplantation. Isolated pancreas transplantation is indicated for T1D patients without severe nephropathy. Prevalence of threat to life with complicated diabetes (severe hypoglycemia) over the possible consequences of prolonged immunosuppression is an obligatory criterion for selection.

For T1D patients with a previously transplanted kidney, subsequent pancreas transplantation is justified in terms of preventing transplant nephropathy and improving the quality of life. Also, an argument in favor of pancreas transplantation after kidney transplantation is the immunosuppression protocol formed and established by this time, which promotes optimum physiological and psychological adaptation of the patient to the upcoming surgery. The necessary condition for pancreas transplantation is stable function of the previously transplanted kidney (creatinine clearance >50 mL/min).

The technical aspects of performing pancreas transplantation at various transplantation centers follow the same principles: ensuring adequate arterial blood supply to the pancreas and duodenum segment, free venous outflow from the transplant and ensuring pancreatic exocrine secretion [14].

Thanks to advances in transplantation technologies and immunosuppression regimens, graft and recipient survival rates have significantly increased. Simultaneous liver-kidney transplant in diabetic patients significantly increases kidney graft and recipient survival in comparison with isolated kidney transplantation [15].

Recipient survival at one year post-transplantation is above 95% for pancreas transplants alone, and 90% at 3 years post-transplantation. One-year graft survival is

85% in combined pancreas/kidney transplant compared to 79% in solitary pancreas transplants [16] and 78–83% in pancreas transplant after kidney transplant [17].

Thus, simultaneous pancreas/kidney transplant is an effective method of treating patients with T1D complicated by end-stage renal disease.

2. Pancreatic islet transplantation

A significant limitation to higher numbers of pancreas transplantation is the unsatisfactory state of pancreas from deceased donors. Moreover, there are no objective criteria for assessing organ complex quality. According to reports from the German registry, three quarters of the reasons for graft rejection are subjective [18].

In case of rejection of whole-organ transplant, technologies have been developed for isolating islet cells for subsequent transplantation to patients with insulin-deficient carbohydrate metabolism disorders.

In 1977, the first successful islet cell autotransplantation (ICT) was performed in Minnesota.

In a number of countries (Canada, Australia, Great Britain, Switzerland, Norway, etc.), islet cell transplantation is a medical care standard "that does not require further scientific justification" [19].

Until 2000, according to the world registry, only 12.5% of patients had euglycemia after pancreas transplantation for more than 1 week, and only 8.5% of patients retained graft function after a year.

In 2000, a paper by Professor Shapiro with co-authors from Edmonton reported that all 7 patients, who underwent ICT according to the implemented protocol, attained sustained insulin independence from 6 to 12 months [20]. The main points of the "Edmonton Protocol" remain generally accepted nowadays:

1. Thorough selection of recipients. The main group of patients who are shown to have the so-called brittle diabetes, characterized by hard-to-control glucose levels, while constant fluctuations from severe hyperglycemia to critical hypoglycemia significantly accelerate patient disability and reduce their lives considerably.
2. Very high dose of islet cell suspension. The standard rule before the Edmonton Protocol was introduced was: 1 donor – 1 recipient. The dose recommended by the protocol is at least 10,000 IEQ/kg with additional administrations in the case of reduced function, which requires the use of 2 to 3 grafts per recipient.
3. Modern immunosuppression regimens. Nonsteroidal therapy, as well as induction with IL-1 and IL-2 inhibitors, showed excellent results in ICT.

Currently, the clinic at the University of Alberta in the Canadian city of Edmonton continues to be the leading research institution in the field of ICT for T1D. The best ICT outcomes are achieved by centers adhering as closely as possible to the standards established in Edmonton [21].

According to the above study, among the 48 study subjects, the primary end point was successfully met by 87.5% at 1 year and by 71% at 2 years. Two years after ICT, the median HbA_{1c} level was 5.6%. No ICT-caused death has been reported. Data were obtained on 50% of the 5-year ICT efficiency in a number of centers, which brings the results closer to whole-pancreas transplantation. Of the current advances that have significantly improved ICT outcomes, the use of alemtuzumab (anti-CD52 antibody) induction and etanercept (TNF inhibitor) to suppress the inflammatory response after ICT should be noted.

Biologically active islet encapsulation in a porous peptide-fragmented alginate structure is a promising technology. Pores allow cells to receive oxygen and nutrients and to freely secrete hormones into the environment. The capsule protects the islets from exposure to immunocompetent cells, which eliminates the need for immunosuppressive therapy and prevents surrounding fibrosis. There is an active search for ways to supplement the extracellular matrix of the pancreas, stem cells, oxygen nanotransporters inside the capsule to increase the efficiency and duration of its functioning.

Donor phase (ICT)

The number of islets obtained, and their quality, largely depend on age, BMI (body mass index), donor, and cold ischemic time.

Most centers routinely examine donors with increased BMI for impaired glucose tolerance, since it is known that obesity is often associated with type 2 diabetes.

Prolonged cold ischemic time lasting for more than 6–8 hours has a negative effect on the dose and quality of the obtained islet cell isolate. It is preferable to use a UW solution for preservation, which does not exclude the use of an HTK solution.

According to some research, it is easier to get adequate dose of cellular isolate in age-related donors (51–56 years old) (83% versus 37% in donors aged 19–28 years), but the secretory capacity of these islets is much lower. Donors in the young age group are considered to be "ideal", but the technically more complex isolate preparation procedure due to the severity of the glandular fibrous structures should be taken into account.

Immediately after introduction of islet cells, 70–80% of their mass turns out to be non-viable even if strict donor selection criteria similar to those for a whole-organ transplant are met [22].

The latest technological advances of the time were used in isolating islet cells at Edmonton:

– splitting of the pancreas using the latest generation of collagenase enzymes (liberase)

– cellular isolation by the automatic method proposed in 1988 by Professor Ricordi. This method allows to minimize cell injury and significantly increase their concentration at the output and the degree of purity of the isolate.
– use of a computerized cell separator, which allows to get rid of fragments of the stroma, exocrine cells, etc from the isolate.

Today, stringent requirements for preparation of ICT materials in a number of countries have led to the creation of single laboratories serving multiple centers to maintain high GMP standards and save resources.

Islet isolation technique

Islet isolation and preservation method begins already during explantation (minimal injury, rapid systemic and local cooling of the pancreas).

The purpose of the pancreatic processing stage is to free the islets from the surrounding extracellular matrix. This is achieved by a combination of mechanical and enzymatic "digestion" of the gland. First, external fat is removed, while special attention is paid to preserving the integrity of the organ capsule. Next, the pancreatic duct is cannulated and a collagenase solution is injected, which allows for 10 minutes to cause swelling of the gland and to separate the islets from the surrounding exocrine tissue. Areas of pancreas that have not been exposed to overstretching are not suitable for further processing. Then the pancreas is cut into several parts and placed in the Ricordi chamber. This closed system maintains constant recirculation of the warm solution containing collagenase, and with the help of hollow metal balls, the gland tissue is mechanically fragmented and filtered through a screen (with 500 μm pores). If the digestion process does not stop after most of the islets have been released, they are rapidly damaged by collagenase. Currently, the most commonly used mixture is Roche's Liberase HI. A disadvantage of this mixture is that it uses clostridial collagenases, and although pathogen transmission risks are negligible, such concerns exist. Alternative mixtures, including those with the ability to regulate collagenase activity, are being tested.

After dissociation of the islets, they must be purified. It is known that introduction of large amount of isolate into the portal vein leads to serious complications up to lethal (thrombosis, embolism). Islet purification is based on the difference in the density of islet and exocrine cells. When placed in a medium with a known density and centrifugation, islet cells, as less dense, occupy the upper layer of the medium. Only a fully automated centrifuge-type separation system can obtain a fraction of islet complexes with high degree of purification (≥70%) [23].

Purified islets are counted in islet equivalents using automatic counters, where 1 equivalent is equal to an islet with 150 μm diameter. Microscopy is performed to assess islet viability. Functionality is assessed using insulin tests, as well as by injecting diabetes into mice. Assessment in the mouse model has the highest correlation with the clinical effect of ICT, but it takes a lot of time and is almost never used at present. Sterility is established by testing for aerobic and anaerobic bacterial cultures, and for mycoplasma and endotoxin [24]. According to the classic Edmonton protocol, the isolate was injected immediately after preparation. However, storing the cell culture for a certain time allows to optimize the logistics (recipient preparation, immunosuppression induction, isolate transportation) and reduce immunogenicity in the medium.

In case of incomplete response, additional infusions are carried out, which requires additional donors for each recipient [25].

Administration technique

Some islet injection locations were studied: under the kidney capsule, in the greater omentum, the anterior chamber of the eye. However, intraportal administration of islet cells is today the standard method in clinical practice. It is minimally invasive and safe. Bleeding and portal thrombosis – the most formidable complications of this operation – occur with a less than 10% frequency and are very rarely fatal.

Islet response to implantation

Positron emission tomography was used to established that immediately after intraportal administration, 50–70% of the islets lose their viability. Therefore, the use of suspension from 2 to 3 donors is necessary [26, 27].

The main damage to islets after administration occurs due to pathological processes developing in the recipient's body. The most studied consequence of intraportal administration of islets is instant blood-mediated inflammatory reaction (IBMIR), which is an immune response developing immediately after transplantation from blood clot formation, and infiltration by mast cells and macrophages [28, 29]. Microthrombi consisting of platelets, neutrophils, and monocytes appear 5 minutes after islet infusion [30, 31]. The response is initiated by a coagulation cascade, which peaks at 6–12 hours after islet infusion [32].

Complementary activation also occurs. Inside and on the surface of islets, C1q, C4, C3, nad C9, IgG, and IgM are determined, which leads to formation of anaphylotoxins C3a and C5a. A set of cytokines stimulates migration and activation of inflammatory cells. Activated thrombin causes endothelial cells to secrete adhesion factors, such as P selectin, resulting in platelet aggregation. Endothelial cells secrete pro-inflammatory interleukins IL-6 and IL-8, which help migrate neutrophils and ma-

crophages into the focus. Monocytes and macrophages help maintain an inflammatory response.

Islet cells undergoing stress caused by hypoxia and injury during isolation provoke inflammation by TF secretion and expression of proinflammatory factors: HMGB, IFNc, IL-6, IL-8, IL-1b, IFNc-induced protein, MCP, tumor necrosis factor (TNF), nuclear factor kappa B (NF-κB), nitric oxide, and others [33, 34].

The search for ways to reduce inflammatory response showed that heparin and low molecular weight dextran sulfate have positive effect. The use of other drugs – nicotinamide, thrombin inhibitors, sCR1 complement inhibitors, C5a inhibitors – is being investigated. Alternative ways of protecting islets by PEGylation and mast cell coating are being studied. In clinical practice now, only heparin is being used routinely and widely [35, 36, 37].

Ischemia-reperfusion injury (IRI) of the islets is difficult to characterize due to lack of possibility of biopsy. Its degree can be indirectly detected and evaluated by transient increase in AST and ALT levels, which is observed in half of the recipients and peaks by the end of the first week after ICT. The systemic effect of IRI after ICT is weakly expressed, but locally it significantly promotes early loss of islet viability [38, 39]. Native islet cells oxygenate very well, consuming 5–15% of oxygen flowing through the pancreas, with about 40 mmHg oxygen tension. Under culture, large islet complexes suffer from hypoxia, which causes central necrosis and apoptosis. During the first days after intraportal infusion, islets are oxygenated only by diffusion in the low oxygen tension portal system, which is exacerbated by coagulation cascade in IBMIR. It takes 7 to 14 days for an autonomous functional blood supply system to be developed using newly formed capillaries. Even after 3 months, oxygen tension does not exceed 5 mmHg. Moreover, hypoxia does not depend only on intraportal location of the islets; studies on introduction of islet cells into more blood-supply areas showed similar outcomes [40, 41].

There is evidence of the positive effect of cycles of blocking and restoring portal blood flow (ischemic preconditioning), which has a protective effect on both the liver and islets.

Immunosuppression in islet cell autotransplantation

Calcineurin inhibitors (cyclosporin and tacrolimus) and steroids (prednisone) were some of the standard immunosuppression regimens used in the late 90s and early 2000s, in fairly large dosages. These drugs provide effective prevention of graft rejection, but have a number of side effects, including toxicity to islet cells. The Shapiro team successfully applied a steroid-free immunosuppression regimen with reduced tacrolimus dose through daclizumab (antibodies to interleukin receptors) induction and addition of sirolimus (proliferation inhibitor) to the treatment protocol.

ICT performance assessment

There is now a paradigm shift in measuring ICT effectiveness as experience is gained. Previously, ICT goal was to achieve and maximize the duration of insulin independence. Currently, ICT is considered a treatment for insufficient beta cell function, regardless of the cause, if the patient has brittle diabetes with problematic hypoglycemia or hyperglycemia, despite optimized medical care. The use of insulin after pancreas or islet transplantation does not indicate a loss of graft function. To maintain glycemic levels, patients may need low doses of exogenous insulin, normalizing blood glucose levels that can be achieved when part of the insulin requirement is supplied endogenously from a functioning graft.

The optimal function of the beta-cell graft is determined by the presence of an almost normal glycemic profile, estimated by the level of glycated hemoglobin (HbA1c) 6.5% or less, absence of severe hypoglycemia, lack of need for exogenous insulin and increased C-peptide level compared with the pre-transplantation level.

A good beta-cell graft function reduces daily insulin demand by 50% (should be <0.5 IU per kg of body weight per day) provided that blood sugar level is adequately controlled (HbA1c <7%) and increase in C-peptide (should be at least 0.5 ng/mL) compared with pre-transplant levels.

The borderline function of a beta-cell graft is determined by inability to reach the target HbA1 level of less than 7.0%, by occurrence of any severe hypoglycemia, or by a less than 50% decrease in insulin demand, despite increased C-peptide level compared to the pre-transplantation level.

If reduced hypoglycemia awareness, frequent severe hypoglycemia or severe glycemic lability, which improved after transplantation, has been documented prior to transplantation, then it may be appropriate to consider the beta-cell graft as having a clinical effect. Clinically, the benefits of maintaining and controlling beta-cell graft function may outweigh immunosuppression risks.

In the absence of evidence of clinical improvement, even with increased quantitative level of C-peptide after surgery, borderline and insufficient beta-cell graft are considered clinically unsuccessful.

Currently, over 60,000 pancreas transplantation and 4,000 ICTs have been performed worldwide. Comparative characteristics of the procedures are presented in the table below.

Thus, ICT technology, with careful adherence to protocol, is good for correcting insulin-dependent carbohydrate metabolism disorders, preventing severe hypoglycemia. In terms of efficiency, it is practically not inferior to

Table

Comparative characteristics of pancreas and islet of Langerhans transplantation

Generalized experience	Pancreas transplantation	Islet cell transplantation
	Over 60,000	Over 4,000
Insulin independence 1 year 5 years	 90% 70%	 60–80% 25–50%
Function (C-peptide 5 years)	70%	70%
Best combination options	SPK > PAK > PTA	SIK, IAK, ITA equivalent
Intervention	Extensive laparotomy	Interventional radiology
Complications	Severe	Rare
Mortality	4–6%	none

whole-organ transplantation. The ICT technology gives higher safety and accessibility.

Pancreatogenic diabetes mellitus

After critical reduction in the mass of pancreatic parenchyma, pancreatogenic diabetes mellitus (PD) develops, which differs from T1D. Total pancreatectomy, pancreatic necrosis, chronic fibrosing diseases, gland atrophy due to chronic inflammation, and tumors may be the reasons for the loss of critical islet mass.

The peculiarities of PD are determined by the lack of function not only of beta-cells, but also of the rest of the endocrine cells of the pancreas. Pancreatic polypeptide deficiency leads to hepatic insulin resistance and increased liver glucose production. However, under endogenous hyperinsulinemia, sensitivity of peripheral tissues to insulin increases, which helps to reduce blood glucose. Lack of glucagon secretion and impaired secretion of intestinal incretins also reduce its level, increasing the risk of hypoglycemic conditions [42]. Episodic hypoglycaemia was experienced by 79% of patients, while 41% experienced severe hypoglycaemia with loss of consciousness [43].

Despite rare development of ketoacidosis and moderate hyperglycemia, PD patients are prone to a labile course with high glycemic variability and repeated severe hypoglycemia. Incidence of chronic micro- and macrovascular complications is the same for T1D and PD.

One of the limiting factors in planning a pancreatectomy is doubts about patient compliance and commitment to subsequent lifelong PD treatment.

Islets autotransplantation after total pancreatectomy

Currently, the ICT procedure, due to its safety, can be considered as a tool for correcting carbohydrate metabolism disorders in planning operations related to total removal of the pancreas (pancreatectomy).

Pancreatectomy is indicated for patients with irreversible common pancreatic diseases. There have been published works on the use of auto-ICT after removal of the pancreas for benign tumors, injury and arteriovenous malformations. The possibility of auto-ICT in ductal adenocarcinoma and intraductal papillary mucinous neoplasm is currently controversial and requires further study [44].

Islet cell autotransplantation in painful chronic pancreatitis

The technology for treatment of chronic pancreatitis pain – total pancreatectomy followed by auto-ICT – is actively developing. With autotransplantation, there is no need for an immunosuppression protocol, thus excluding the negative effects of immunosuppressive therapy after ICT.

Performed for the first time in 1977 by Sutherland et al (University of Minnesota, USA), pancreatectomy with islet cell autotransplantation allowed the patient to get rid of pain and stay in a state of euglycemia for 6 years, after which he died from causes not related to the underlying disease. Such a result aroused great interest in the world and to date, there have been more than a thousand operations [45]. The main patient population for the TPIAT procedure includes people with painful chronic pancreatitis who need constant pain relief.

Prevalence of chronic pancreatitis (CP) is quite high. Annually in the USA, depending on the region, 4–12 new cases are detected per 100,000 population. In Europe, prevalence of chronic pancreatitis ranges from 4 to 40 cases per 100,000 population [46, 47, 48]. In Russia, it is up to 30 new cases per 100,000 population [49].

Idiopathic pancreatitis is the second most common and it is mainly caused by genetic conditions – associated with mutations in the PRSS1, CFTR, SPINK1, and CTRC genes [50, 51].

The most pronounced clinical manifestation of CP is constant or intermittent pain in the upper abdomen, which is observed in 85–90% of patients, It leads to significant deterioration in quality of life, up to constant prescription of narcotic drugs [44, 52, 53].

In conservative management of CP patients, the drugs of choice are analgesics, predominantly opioid-based. They suppress pain well, but cause dependence, and, with prolonged use, lead to many serious side effects. In USA, where opioid therapy is most common, 26,000 deaths from the effects of opioid prescribed by doctors are recorded annually [54].

Total pancreatectomy with autotransplantation of pancreatic islets is most effective in patients with unexpanded pancreatic duct and in patients with hereditary pancreatitis [55].

Most researchers agree that, if there are indications, the operation should be performed as soon as possible. Previous pancreatic drainage surgeries and a long course of pancreatitis significantly affect the received dose and quality of islet cells [56].

This treatment method is based on total removal of the pancreas as a source of persistent pain with subsequent islet autotransplantation, most often into the portal vein [57]. Such surgical interventions have been steadily increasing in number recently [58, 59, 60]. The vast majority of centers show zero mortality after surgery; it does not exceed 1% in the general analysis [61, 62]. The outcomes of such interventions are evaluated on the basis of changes in the quality of life: disappearance of pain and reduced need for opioids, prevention of hypoglycemia. Achieving insulin independence is not an end in itself [63].

The number of patients who got rid of drug dependence after pancreatectomy with islet autotransplantation varies from 35 to 100% (on average above 60%) during a 12–24-month follow-up. The remaining patients noted significant reduction in opioid dosage and transition from daily to episodic pain medication. Analysis of the pain scale showed a change from 60–100 (out of 100) points to 8–20 (100) within 1 year. This effect may persist for a long time. Approximately 73% of patients remain independent of analgesics for more than 5 years [61].

Despite the fact that insulin independence is not long-term stable in 15–41% of patients, euglycemia continues for 6–12 months.

Currently, it is believed that surgery is indicated for patients who fall under the following five criteria [62, 63]:

1. Chronic pancreatitis with pain lasting for more than 6 months amid one of the following symptoms:
   - Presence of pancreatic calcifications in CT.
   - At least two of the following symptoms: 4 or more criteria out of 9 according to endoscopic ultrasonography; changes in the pancreas duct and pancreatic parenchyma in magnetic resonance cholangiopancreatography; changes in the endoscopic pancreatic function test (peak value of Hco2 ≤80 mM).
   - Diagnosis of chronic pancreatitis confirmed by histopathological examination.
   - Appropriate history and documented hereditary pancreatitis (PRSS1 gene mutation).

   Or
   - Past history of recurrent acute pancreatitis (more than one episode of an attack of characteristic pain in combination with changes in instrumental studies and/or a three-fold or more increase in serum amylase or lipase).
2. One of the following symptoms:
   - Daily need for narcotic analgesics.
   - Decreased quality of life associated with pain (inability to attend school, repeated hospitalizations, inability to perform activities appropriate to age).
3. Currently confirmed or untreated pancreatitis without obvious cause.
4. No effect from drug therapy and endoscopic treatment methods.
5. Adequate islet functioning (no diabetes or positive C-peptide).

Patients with diabetes on the background of negative C-peptide, who meet criteria 1 to 4 are shown to perform total pancreatectomy without autotransplantation.

The following are considered as relative contraindications [58]:

1. Existing T1D or PD.
2. Steatohepatitis.
3. Portal vein thrombosis.
4. Portal hypertension.
5. A past history of longitudinal pancreatico-jejunostomy.
6. Visceral hyperalgesia.
7. Psychological disadaptation.

When evaluating a candidate for pancreatectomy with islet autotransplantation, it is necessary to take into account that age-related changes, alcohol, smoking, diabetes and obesity can cause fatty degeneration and pancreatic atrophy in combination with pain under the mask of chronic pancreatitis [64]. At the same time, prolonged use of narcotic analgesics can lead to functional changes in the intestines and central nervous system, which are difficult to diagnose and treat, but can affect surgical outcomes [65, 66]. It has been proven that long-term outcomes of surgical treatment of patients with hereditary chronic pancreatitis are significantly better than in patients who abuse alcohol [75, 76].

An important factor in preoperative examination is the evaluation of the endocrine function of the pancreas even in the absence of confirmed diabetes. Glucose tolerance test is easily reproducible, but its results do not correlate with the volume of the unaffected islet apparatus [69]. More effective for indirect estimation of the volume of functioning islet apparatus is a method for assessing the secretion of insulin and C-peptide induced by arginine [70].

Treating a patient with chronic pancreatitis is very expensive [71]. Moreover, studies conducted in the UK showed the cost-effectiveness of total pancreatectomy with islet transplantation in comparison with traditional methods of treating chronic pancreatitis [72].

A currently adopted multicenter clinical protocol for islet transplantation named “07”, includes the following

components necessary in the postoperative period after autotransplantation [73]:
- Timoglobulin.
- TNF-alpha inhibitor (etanercept).
- Heparinization.
- Insulin therapy for 8 weeks of the perioperative period.
- Tacrolimus and sirolimus as in the Edmonton Protocol [74, 75, 76].

Pancreatectomy with islet autotransplantation improves quality of life in patients. Most patients get rid of severe pain. Various authors have reported that up to 79% of patients do not need narcotic analgesics after surgery [63, 77]. In addition, patients do not require insulin therapy in a significant number of cases in a long-term postoperative period [78, 79].

CONCLUSION

Type I diabetes and pancreatogenic diabetes mellitus are a huge social problem around the world. The only available massive way to control blood sugar levels is by administering exogenous insulin. Improving insulin therapy, creating new convenient and genetically "close" insulins, and pump therapy remain only a symptomatic treatment that has certain shortcomings, such as disabling complications and fatal hypoglycemia.

Transplantation technologies for the treatment of severe insulin-dependent carbohydrate metabolism disorders are promising due to their high efficiency and safety. The advantage of using transplant technology is down to the delicate biological inverse relationship between serum glucose levels and insulin production by beta cells.

General shortage of donor organs and insufficient quality of received pancreas for transplantation necessitate development of ICT technology. Analyses of whole-organ transplantation and islet suspensions show similar efficacy with greater safety of the ICT procedure. The first achievements in the field of bioactive islet encapsulation give the procedure significant advantages – no immunosuppressive therapy. Encapsulation also allows for long-term functional activity of the islets.

In the Russian Federation, actions are required to legally legitimize the ICT procedure (introduction of islets of Langerhans in the list of organs and tissues for transplantation).

The technologies of allo- and autotransplantation of cell cultures of pancreatic islets are similar and are derivatives of the same protocol. It is advisable to create specialized and certified laboratories for isolation and storage of islets. The technical features of performing pancreatectomy do not present difficulties for doctors at a specialized pancreatological center. Implementation of a pancreatectomy protocol with islet autotransplantation will improve treatment outcomes for a large group of patients with chronic pancreatitis.

The study was supported by the Ministry of Health of the Russian Federation (state assignment on the "Creation of technology for encapsulating pancreatic islets compensating for absolute insulin-deficient states").

The authors declare no conflict of interest.

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The article was submitted to the journal on 16.01.2020