Pancreas Transplantation

This article is devoted to pancreas transplantation from the point of view of diabetology. Transplantation of the pancreas or islets in patients with type I diabetes mellitus, unlike insulin therapy, leads to almost complete long-term normalization of blood glucose without hypoglycemic states. However, it is not suitable as a method of first choice for all patients with this disease. Currently, pancreas transplantation remains the only method that immediately after surgery induces a normoglycemic state, stabilizes the value of glycated hemoglobin, and is capable of stabilizing or even regressing microvascular changes in diabetes with long-term good function of the graft.

History

The world

The first attempts to treat type I diabetes mellitus with pancreas transplantation took place at the turn of the 19th and 20th centuries. These attempts were unsuccessful, as they came up against the technical and immunological barriers of the time. It wasn't until December 17, 1966, at the University of Minnesota in Minneapolis that Kelly and Lillehei performed the first combined kidney and pancreas transplant in a human. The pancreas transplant program has always been closely linked to kidney transplants, as diabetic nephropathy has always been a significant complication of diabetes itself. However, the results of these operations were not very satisfactory. Patients often suffered from complications associated with imperfectly treated exocrine secretion such as infections, thrombosis, dehiscence and fistulae. At the turn of the 1970s and 1980s, clinical testing of Cyclosporin A allowed the development of pancreas transplants to be accelerated. An equally important role was played by the organization of several international congresses dedicated to pancreas transplantation, which mainly solved problems related to the solution of exocrine secretion using urinary drainage or Roux-en-Y duodeno-jejuno-stomy. However, urological drainage later turned out to be burdened by a greater number of urological and metabolic complications, so after the further development of immunosuppressive treatment, the bowel drainage technique was preferred. In order to avoid a non-physiological increase in insulin in the vascular bed after connecting the venous system of the graft to the veins of the pelvic system (and thus to accelerate atherogenesis), even today, in half of the world's centers, preference is given to connecting the venous system of the graft to the portal bed. In most cases, the graft was implanted into the body retroperitoneally, but at IKEM they also developed a method of extraperitoneal implantation of the graft.[1] [2]

Czech republic

By the mid-1970s, doctors at IKEM had enough experience with kidney transplants to attempt to combine this procedure with a pancreas transplant. Similar to the world, it was necessary to solve primarily the exocrine drainage of the pancreas. At IKEM, after experiments on dogs, they chose the technique of early obliteration of the outlet using a polymer. This technique has the advantage (compared to a ligature) that there is no congestion, subsequent rupture (and necrosis/thrombosis) and the formation of a fistula in the drainage system. Acini are also inhibited and produce less digestive enzymes. Subsequent microscopic verification revealed that between the 35th day and the 10th month, the pancreas fibrotizes and the gland with internal and external secretion becomes a gland with mainly internal secretion. The best results were obtained using an autograft segment with supply vessels. Thanks to the knowledge gained from the experiments, the first combined pancreas and kidney transplant in humans was performed in the Czech Republic in 1983. Ultimately, the results of these operations did not live up to expectations, so it was clear that new techniques would have to be sought. Long-term results changed fundamentally with the introduction of whole pancreas transplantation with bladder drainage in 1994. Urological and metabolic complications (dehydration and large bicarbonate losses and associated acidosis) due to their relative frequency limited the further development of whole pancreas transplantation with bowel drainage around 2000 , as was common in the world at this time. Langerhans islet transplantation has been performed at IKEM since 2005. [1][3]

Indication

As with all operations, the risks and benefits need to be weighed. Considering the risks associated with long-term immunosuppression, the operation is mainly reserved for patients who are waiting for a kidney transplant or for patients who have already undergone a kidney transplant. A non-immunosuppressed patient's indication for the procedure may be impaired perception of hypo/hyperglycemia - i.e. if the risks of poorly compensable diabetes outweigh the risks of long-term immunosuppression. In such a case, an isolated pancreas transplant can be performed. Another indication for isolated transplantation is diabetes causing rapid development of microvascular complications. Combined kidney and pancreas transplantation is indicated in the case of terminal diabetic nephropathy. About 95% of patients are indicated for diabetes mellitus type I, a minority for diabetes mellitus II. type. In IKEM, patients with diabetes II are indicated. type for combined transplantation only in case of BMI below 30kg/m2, if they need more than 0.7 units/kg of insulin and at the same time if insulin therapy is unsatisfactory. In Europe, only organs taken from cadaveric donors are used. In general, there is no age limit in case of indication for transplantation, but isolated transplantation is rarely performed above 50 years of age and combined transplantation above 60 years of age. Contraindications to transplantation are ischemic diseases of the heart, CNS and lower limbs, especially with developed diabetic foot syndrome.[1]

Surgical technique

The complications of urological drainage described above were responsible for the development of enteral drainage. Transplantation of the whole organ is preferable to segmental transplantation, which has led to a reduction in the number of complications in the form of thrombosis, graft pancreatitis and fistulas. At the same time, a larger mass of Langerhans islets is transplanted. The surgical approach is either **extraperitoneal** from an oblique incision in the right lower quadrant of the abdomen, or **intraperitoneal** most often from a longitudinal laparotomy. The first one carries with it a significantly increased risk of postoperative peritonitis and possible other infections, but it allows better absorption of fluid around the gland. The latter (in the Czech Republic, carried out by IKEM) brings good results burdened by often impaired healing of the surgical wound. Venous anastomosis can be performed either on the right girdle of pelvic veins (given by anatomical conditions) or, in the case of intraperitoneal transplantation, on the portal bed. The theoretical advantage of the latter procedure is the prevention of non-physiological levels of insulin and the development of tolerance. In practice, however, no influence on carbohydrate metabolism has been demonstrated. After harvesting the graft, it is often necessary to reconstruct the arterial bed of the graft. The anastomosis is usually established with the end to the side on the right external pelvic artery. During reoperation, also on the common pelvic artery or aorta. The most common technique for dealing with exocrine secretion is enteral drainage - connecting the duodenum graft to the jejunal loop. A Roux-en-Y loop or direct connection elsewhere can also be used. Connection to the bladder is no longer used much due to the occurrence of complications.[1]

Complication

- surgical - thrombosis, bleeding, leakage of pancreatic juice, pancreatitis
- hematological - anemia, erythrocytosis, myelotoxicity
- urological - hematuria, bladder infection
- metabolic - acidosis, dehydration
- gastrointestinal - diarrhea, gingival hyperplasia, ulceration in the oral cavity

Surgical complications

About 5% of patients develop **thrombosis of the graft vessels**, which is also the most common surgical complication. Venous occlusion occurs more often than arterial occlusion. Postoperative anticoagulant therapy and long-term antiplatelet therapy can be used as prevention. In case of blockage, thrombolytics must be used. Another complication is **bleeding.** Its source is usually vascular anastomoses and surgical revision is necessary. **Leakage of pancreatic juice** is described in up to 10% of cases. A technical error is usually to blame, and if it cannot be managed conservatively, surgical revision is necessary. The picture is similar to acute pancreatitis with fever and leukocytosis. **Graft pancreatitis** is a rare complication.[1]

Hematological complications

Most patients come to the transplant with already secondary anemia. The persistence of this anemia may be the result of poor graft function or as a reaction to treatment with azathioprine or other immunosuppressants. After the operation, the hemoglobin value gradually normalizes. However, an excess of hematocrit may be present as a response to surgery. This erythropoiesis is due to an increase in IGF (insulin-like growth factor) and its binding protein IGF-BP (insulin-like growth factor binding protein) rather than the originally considered increase of EPO in the peripheral blood. Increased erythropoiesis may endanger the patient by increasing the risk of pulmonary embolism. Azathioprine may have a **myelosuppressive effect.** Today, mycophenolate mofetil is usually replaced by mofetil, which should not have an effect on the proliferation of the myeloid line - the incidence of anemia and leukopenia during treatment is, however, similar. Also, some antiviral and antibacterial drugs (trimethoprim-sulfamethoxazole, acyclovir, gancyclovir) can have a myelotoxic effect.[1]

Urological complications

Hematuria appears after surgery in three forms according to severity. The mild form disappears spontaneously within 2-3 days after the operation. The more severe form is not usually life-threatening, it only makes the healing and vascularization of the patient uncomfortable. It is usually sufficient to interrupt pharmacotherapy with acetylsalicylic acid, or perform a flush. Chronic hematuria appears 4-6 weeks after surgery and may persist for several years. The cause is usually an ulcerative lesion in the mucosa of the duodenal segment after chronic CMV infection. If the hematuria persists, a surgical solution is necessary, possibly even the establishment of a permanent urinary drainage to the intestine. Bladder infections are most often observed in patients with this type of drainage - today, therefore, rather rare.[1]

Metabolic complications

Bladder drainage was associated with high bicarbonate loss and dehydration. This led to metabolic acidosis and gradual transition to enteral drainage. However, these symptoms can also be accompanied by enteral drainage in case of insufficient function of the kidney graft.[1]

Infectious complications

An immunosuppressed patient is at risk of a higher risk of opportunistic infections. In terms of time, 3 phases can be distinguished: the early postoperative phase - the first 4 weeks - patients are at risk mainly from infections present in their organism before the operation, infections from the graft or medical material. Middle phase - in the first half of the year, the patient is mainly at risk of CMV, EBV, VHB and HIV infections. Late postoperative phase - approx. 50% of patients have similar risks as members of the general population (i.e. primarily respiratory and urinary infections), in addition to the infections listed in the second phase, others are also at risk of P. carinii, Listeria monocytogenes, etc. Therefore, they require increased and long-term antimicrobial therapy .[1]

Gastrointestinální komplikace

A frequent postoperative complication is **diarrhea**, regardless of the use of immunosuppressants or antibiotics. Another complication can be **gingival hyperplasia or ulceration in the oral cavity** as a reaction to the use of specific immunosuppressants (Cyclosporin A, sirolimus).[1]

Transplantation of islets of Langerhans

The benefits of pancreas transplantation are somewhat overshadowed by late microvascular complications. The goal of therapy using the transplantation of insulin-producing tissues from alternative sources is to improve the quality of life of patients as well as to prevent late complications and possible side effects of pharmacotherapy. Transplantation of the islets of Langerhans is currently the only clinically applicable alternative to organ transplantation, but it complements it, as islets from obese and elderly donors unsuitable for organ transplantation can be used in particular. The disadvantage compared to organ transplantation is the lower yield of islets, which are isolated gradually, and a part of the previously isolated ones is thus subject to hypoxia and mechanical degradation. The yield of islets from one donor does not cover the metabolic demands of one recipient. Usually, pancreases from 2-3 donors need to be used per recipient. The costs of organ and islet transplantation are comparable, the long-term success rate of islet transplantation is gradually approaching that of organ transplantation, but for now it is close to 80% long-term success rate. Pancreas transplantation has a long-term success rate of between 80-90%. Indications for surgery are similar to those for organ transplantation - primarily type I diabetics with repeated unrecognized life-threatening hypoglycemia or difficult-to-manage glycemic decompensation. Contraindicated are patients with diabetic nephropathy (due to the toxicity of immunosuppressants) and sometimes also obese patients - the amount of islets is injected as IEQ/kg, where IEQ is the islet equivalent (the amount of tissue corresponding to an islet with a diameter of 150 μm).[1]

History

The first idea to transplant islets is attributed to the Russian scientist Sobolev sometime around 1902. It was not until the late 1960s that clinical research into islet transplantation was conducted in Minneapolis. At first, a very promising treatment was supposed to completely replace organ transplantation. Later it became clear that although this method is burdened with fewer complications, it is more difficult to extract the islets. During extraction, many of them succumb to hypoxia and mechanical effects, subsequent post-implantation hypoxia (before they form blood vessels), moreover, the immunogenicity of islets is comparable to the whole organ. It is also necessary to extract islets from more than 1 donor pancreas for one recipient. The first successful transplantation was performed by Largiader et al. in Zurich in 1978. The definition and acceptance of the Edmonton protocol together with the improvement of cell separation techniques (Ricordi 1988) and the development of new immunosuppressants have a high share in increasing the success rate of islet transplantation treatment.[1]

Islet isolation

The isolation itself is preceded by the removal of the organ, which, due to the cost of the entire operation, is ensured by experienced and specialized teams. In 2000, the world's leading workplaces (including IKEM) adopted the principles of a uniform procedure, the so-called Edmont Protocol. The organ must be sufficiently cooled. The preparation of the duct is followed by intraductal injection of collagenase solution and mechanical disruption by shaking in a special chamber. The rate of tissue disintegration depends on the tissue, the activity and quality of the enzymes, etc. The subsequent tissue suspension is further processed and purified in a cell separator based on the different mass of the cells after binding the separation solution. This step is very important because it causes less of an immune response and also reduces the risk of complications such as portal hypertension or DIC.[1]

Islet transplantation

The only clinically used method is injection into the portal tract. Transhepatically, by cannulation by skin puncture or after a small laparotomy by puncturing the mesenteric vein. The transhepatic approach is less invasive, but is associated with a higher risk of bleeding and the need to use heparin. The skin injection is performed under local anesthesia using the Seldinger method directly into the portal vein. The islets are first resuspended in a mixture of albumin and heparin. Before the islet injection itself, it is necessary to verify the location of the injection with a contrast agent. The application itself takes about 5-10 minutes. The peripheral branch used for cannulation can be embolized to prevent postoperative bleeding. After transplantation, it is necessary to continue insulin therapy so that the newly implanted islets are not damaged by high glucose levels. Patients are further treated with immunosuppressants, just as in the case of organ transplantation.[1]

Future

Due to the lack of donors, organ transplantation will probably never become a widespread method of treating diabetes. In the Czech Republic alone, about 25 pancreases are removed annually. It is estimated that only about 40 pancreases for islet isolation could be obtained per year. This amount is necessary for transplanting 10-15 recipients. Certain hopes are placed in the transplantation of animal islets of Langerhans or genetically modified insulin-producing cells with induced immunological tolerance. Thanks to this, this form of treatment could also be used in the treatment of type II diabetes. type.[1]

Alternative sources

Currently, one can only theoretically consider **pig tissue or the development of one's own genetically modified insulin-producing cell lines**. Leaving aside the unclear amount of risk of transmission of porcine endogenous retroviruses, the immunological barrier of xenogeneic tissue still remains higher than that of allogeneic tissue. Modified cell lines must meet many criteria:

- effective growth with the possibility of subsequent inhibition
- sufficient insulin production
- controlled secretion of insulin depending on the body's needs
- low or no immunogenicity

Genetically modified insular or non-insular cells, transformed B-cell lines, embryonic stem cells, and tissue-specific stem cells come into consideration. The technique of differentiating stem cells into cells resembling B-cells of the pancreas, which responded to glucose concentration by producing insulin, was successfully described in animal models. Lifelong turnover of pancreatic B-cells has been demonstrated in humans. Gradually, a number of signaling genes and their products were discovered, which control the differentiation of tissue-specific stem cells. Knowledge of differentiation mechanisms or artificial modification of cells could lay the foundations for mass production of B-cells as an alternative source of insulin-producing tissue in the future.[1]

BioHub

BioHub is a bioengineering project of the DRI (**Diabetes Research Institute**), which aims to mimic the physiological function of the pancreas. It is a miniature device implanted in the body between the layers of the omentum, containing insulin-producing cells that are able to respond to the concentration of glucose in the bloodstream and thus release only the necessary amount of insulin. Some patients may benefit for decades. Compared to islet transplantation, this method has greater universality: there should be no destruction by the immune system; better oxygenation of the cells inside the BioHub until they form their own blood vessels; better cell nutrition. BioHub tries to mimic the physiological environment of the pancreas as faithfully as possible. In addition, it provides the possibility of additional oxygenation or auxiliary cells, which improve the long-term life of insulin-producing cells, reduce the inflammatory reaction and unwanted immune reaction. As such, the BioHub can also be populated with other types of cells. It is possible to apply immunosuppressive substances locally directly into the preparation - this way there is no systemic influence. [3] [4]

Links

related articles

- Pancreas
- Type 1 diabetes mellitus (endocrinology)
- Immunosuppressants
- Islet of Langerhans (SFLT)
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- Transplantation in diabetology

Source

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