Pancreas transplantation

This article is about pancreas transplantation in diabetology. A pancreas or islets transplantation leads to long-term normoglycaemia without hypoglycemic episodes in pacients with type 1 diabetes, unlike the insulin therapy. However, it is not suitable for every pacient with this disease. Today, pancreas transplantation is the only method which induces normoglycemia immediately after the surgery, stabilises glycated hemoglobin and with a long-term functioning transplant also stabilises or even regresses diabetic microvascular changes.[1]

History

World

First attempts to treat type 1 diabetes with pancreas transplantation took place at the turn of the 19th and 20th century. Those attempts were unsuccesful, because they encountered the technical and imunological barriers of those times. Finally on 17th December 1966 at the University of Minnesota in Minneapolis, Kelly and Lillehei carried out the first succesful combined pancreas and kidney transplantation in a human. The pancreas transplantation program has always been tightly connected to the kidney transplantation, because the diabetic nephropathy has always been a severe complication of diabetes. However, the results of the surgeries were not satisfactory. Pacients often suffered from complications connected to poorly treated exocrinous secretion such as infections, trombosis, dehiscences and fistula. At the turn of the 70s and 80s, clinical testing of cyclosporine A accelerated the development of the pancreas transplantation. Organizing several international congresses devoted to pancreas transplantation also played an important role. They were focused mainly on solving problems of exocrinous drainage of pancreas with urinal drainage or the Roux-en-Y duodenojejunostomy. Urological drainage showed a lot of urological and metabolic complications later, so after the development of immunosuppresive treatment, the technique of drenage to the intestine became the preffered option. To prevent unfysiological increase of insulin in the vascular system after connecting the venous system of the graft to the pelvic veins (causing acceleration of atherogenesis), connecting the venous system of the graft to the portal system is preffered today in about a half of world’s centers. In the majority of cases the graft used to be placed retroperitoneally, but they also invented a method of extraperitoneal placement in IKEM.[1] [2]

Czech Republic

In the middle of the 70s, doctors in IKEM had enough experience with a kidney transplantation to try to connect this surgery with a pancreas transplantation. Similarly to the rest of the world, it was neccessary to solve the exocrinus drainage of the pancreas first. After trying out on dogs, they chose the technique of an early obliteration of the outlet with a polymere. This technique has an advanatage to tying. It does not cause congestion and a following rupture (and necrosis / trombosis) and forming of a fistula in the outlet system. Also the acini are inhibited and produce less digestive enzymes. Microscopy control that followed showed that the pancreas fibrotises between day 35 and 10 months and that the previous both exo and endocrinous gland becomes mainly endocrinous one. Best results were achieved using a segment of autotransplant with supplying vessels. Thanks to knowledge from previous attempts, the first transplantation of a kidney and a pancreas in the Czech Republic was succesfuly performed in 1983. Results of these surgeries did not fulfill the expectations, so it was clear that new techniques need to be found. Long term effects changed greatly with the onset of transplantation of the whole pancreas with drainage to the urinary bladder in 1994. Urological and metabolic complications (dehydration, big loss of bicarbonate and connected acidosis) caused around the year 2000 slowing down of the development of the whole pancreas transplantation with the drainage to the intestine, as it was common in the rest of the world. The Langerhans islets transplantation has been performed in IKEM since 2005.[1][3]

Indication

As in all surgeries, it is neccessary to consider risks and benefits. Considering the risks with a long-term immunosuppresion, the surgery is reserved mainly for pacients waiting for a kidney transplant or for those who already underwent it. The indication of a non-immunosuppressed pacient for the surgery could be a broken perception of hypo/hyperglycaemia – so when the risks of badly compensated diabetes outweigh the risks of long-term immunosuppression. In that case, it is possible to transplant the pancreas separately. Another indication for a separate pancreas transplantation is a diabetes causing quick qrowth of microvascular complications. Combined transplantation of kidneys and a pancreas is indicataed in the case of a terminal diabetic nephropathy. Approximately 95 % of pacients undergoing the procedure are diagnosed with type 1 diabetes, the rest are type 2 diabetes. In IKEM, pacients with type 2 diabetes are indicated only if their BMI is under 30 kg/m2, if they need more than 0,7 j./kg of insulin and at the same time the insulin therapy is not satisfactory. In Europe, only the organs form cadaverous donors are used to transplant. Generally, there is no age limit in indication to transplantation, however, isolated transplantation is hardly ever performed over 50 and the combined transplantation over 60 years of age. Contraindications to transplantation are ischemic diseases of the heart, the CNS and the lower limbs, expecially with a developed diabetic foot syndrome.[1]

Surgical technique

Complications of the urological drainage mentioned above caused a development of the enteral drainage. Transplanting the whole organ rather than a segment is preferred and it also leads to a decreased number of complications such as trombosis, pancreatitis in the graft and fistula. Another benefit is that a bigger mass of the Langerhans islets is transplanted. Surgical approach is either **extraperitoneal** from a diagonal incision in the right lower abdominal quadrant, or **intraperitoneal** , usually from a longitudinal laparotomy. The first mentioned has significantly increased risk of postsurgical peritonitis and other possible infections, but allows better absorption of liquid near the gland. The second option (in Czech Republic performed by IKEM) brings better results often loaded with worsened healing of the surgical wound. Venous anastomosis can be done either to the right pelvic plexus (considering the anatomical ratios), or, in the case of intraperitoneal transplantation, to the portal system. Theoretical advantage of the second approach is a prevention of the unfysiological levels of insulin and the creation of tolerance. However, influence of the glycid metabolism was never proven. It is often neccessary to reconstruct the arterial system after the graft collection. Anastomosis is often established with the end to the side to the right external iliac artery, in resurgery even to the common iliac artery or the aorta. The most common technique of solving the exocrinous secretion is the enteral drainage – connecting the duodenum of the graft to the jejunal loop. It is possible to use the Roux-en-Y loop or the direct conection elsewhere. Connection to the urinary bladder is not widely used anymore due to complications rate.[1]

Complications

- surgical - trombosis, bleeding, leacage of pancreatic fluid, pancreatitis
- hematological - anemia, erythrocytois, myelotoxicity
- urological - hematuria, urinary tract infections
- metabolic - acidosis, dehydration
- gastrointestinal - diarrhea, gingival hyperplasia, ulceration in the oral cavity

Surgical complications

About 5 % of the pacients develop **trombosis in the graft vessels**. It is also the most frequent surgical complication. The venous trombosis is more frequent than the arterial. It is possible to use postsurgical anticoagulant therapy and a long-term antiaggregation therapy as a prevention. In case of trombosis it is neccessary to use trombolytics. Another complication is **bleeding**. The source is usually the vascular anastomosis and a surgical revision is needed. **Leakage of the pancreatic fluid** occurs in 10 % of cases. It is usually due to technial error and if not treatable conservatively, a surgical revision is needed. The clinical picture is similar to acute pancreatitis with fever and leukocytosis. **Pancreatitis of the graft** is a rare complication.[1]

Hematological complications

Most of the pacients comes to transplantation already with secondary **anemia**. Persistance of this anemia can be a result of a badly funcioning graft or a reaction to azathioprin or other immunosuppression. After the surgery, the hemoglobin level slowly normalises. Increased hematocrite can be present as a reaction to the surgery. This erythropoesis is more likely caused by an increased IGF (insulin-like growth factor) and its binding protein IGF-BP (insulin-like growth factor binding protein) rather than the previously considered increased EPO in the periferal circulation. Increased erythropoesis can cause a higher risk of developing a pulmonary embolism. Azathioprin can have **myelosuppressive effect**. Today it is substituted with mycophenolat mofetil, which should not affect the myeloid proliferation, however, the incidence of anemia and leukopenia is similar. ALso some antivirotics or antibiotics (trimethoprim-sulfamethazol, acyclovir, gancyclovir) can have a myelotoxic effect.[1]

Urological complications

Hematuria appears after surgery in three forms according to severity. The mild form goes away spontaneously 2 or 3 days after surgery. A more severe form is not life-threatening, but it makes the healing and cathetrisation worse. It is usually enough to stop farmacotherapy with acetylsalicylic acid, or, if necessary, rinse. Chronic hematuria appears 4-6 weeks after the surgery and can persist for several years. The cause is usually an ulcerous leision in the mucosa of the duodenal segment after a chronic CMV infection. If hematuria persists, surgical intervention is necessary, eventually a foundation of a permanent urinal drainage to the intestine. **Urinal infections** are the most frequent in patients with this type of drainage, so it is seen rarely today. [1]

Metabolic complications

Drainage to the urinary bladder was connected to a great loss of bicarbonate and dehydration. That lead to metabolic acidosis and a slow transition to the enteral drainage. Those symptoms can be present with the enteral drainage as well, when the insufficiency of the kidney graft occurs.[1]

Infectious complications

An immunosuppressed pacient is in a greater danger of oportunous **infections**. It is possible to distinguish 3 phases: early post-surgery phase – first 4 days – pacients are endangederd mainly by infections already present in their organism before the surgery, infections form the graft or from the medical supplies. The middle phase – the first 6 months the pacient is endangered mainly by CMV, EBV, VHB and HIV infections. The late post-surgery phase – approximately 50 % of pacients have similar risks as normal population (mainly respiratory and urinary tract infections), others are endangered (apart form the infections mentioned in the middle phase) with *P. carinii, Listeria monocytogenes* etc. They require higher and long-term antimicrobial therapy.[1]

Gastrointestinal complications

Frequent post-surgery complication is **diarrhea** with no connection to using immunosuppression or antibiotics. Another complication is **gingival hyperplasia** or **ulceration** in the oral cavity as a reaction to using specific immunosuppression (cyclosporin A, sirolimus).[1]

The islets of Langerhans transplantation

Benefits of the pancreas transplantation are shaded by the late microvascular complications. The goal of the therapy with the insulin producing tissue transplantation from alternate sources is to improve the quality of pacients‘ lives as well as to prevent late complications and possible side effects of farmacotherapy. The islets of Langerhans transplantation is today the only clinically usable alternative to an organ transplantation, which complements it, because especially islets of obese and older pacients, who are unsuitable for an organ transplantation, can be used. A disadvantage to an organ transplant is lower yield of the islets, which are isolated gradually and part of the earlier isolated ones are affected by hypoxia and mechanical degradation. The islets yield from one donor does not cover metabolic claims of one recipient. Usually it is necessary to use a pancreas from 2-3 donors for one recipient. The costs of the organ and the islets transplantation are comparable, long-term success of the islets transplantation is coming closer to the organ transplant, but for now it is close to 80 % long-term success. Pancreas transplantation has a long-term succes between 80 to 90 %. Indications for the surgery are similar to the organ transplant – mainly pacients with type 1 dibetes with repeted unrecognised live-thretening hypoglycemia or hardly managable glycemic decompensation. Contraindicated are pacients with diabetic nephropathy (because of the toxicity of the immunosuppression) and often also obese pacients – the number of the islets is injected as IEQ/kg, where IEQ is the islets equivalent (the tissue mass corresponding to an islet of 150 um in diameter).[1]

History

The idea to isolate the islets is attributed to a russian scientist Sobolev around the year 1902. At the end of the 60s the first clinical research on the islets transplantation was performed in Minneapolis. A very promising treatment at first was supposed to completely replace the organ transplantation. Later, it showed that even though this method is burdened with less complications, to extract the islets is harder. During the extraction a lot of the islets undergo hypoxia and mechanic impacts, followed with postimplanting hypoxia (before the vessels are created), moreover, the immunogenity of the islets is comparable to the whole organ. Also it is necessary to exctract islets from more than one donor pancreas for one recipient. The first succesful transplantation was performed by Largiader and co. in Zurich in 1978. A great deal at the increase of succes of the islets transplantation therapy has the defining and accepting of the Edmont protocol together with the improvement of techniques of cell separation (Ricordi 1988) and a development of new immunosuppression.[1]

The islets isolation

The isolation itself preceeds the organ resection, which, considering the costs of the whole surgery, is provided by special teams. In 2000 the world’s best clinics (including IKEM) accepted the principles of a uniform procedure, the Edmont protocol. The organ must be cold enough. After the outlet preparation the intraductal injection of colagenase dilusion and a mechanical disolution done by shaking in a special cammer follows. The speed of the tissue dissolution depends on the tissue, the activity and quality of the enzymes etc. The tissue suspension is then processed and cleaned in a cell separator according to a different weigh of he cells after binding the separation dilusion. This step is very important, because it causes less immune response and also decreases the risk of complications such as portal hypertension or DIC.[1]

The islets transplantation

The only clinically used method is the injection in to the portal system. Transhepatally, skin puncture cannulation or after a little laparotomy with punction of a mesenteric vein. Transhepatal approach is less invasive, but is connected with higher risk of bleeding and the need to use heparin. Skin puncutre is performed in local anesthesia using the Seldinger’s method directly into the portal vein. The islets are at first resuspended in a mixture of albumin and heparin. Before the injection of the islets it is necessary to ensure the location of the injection site with the contrast fluid. The application itself lasts about 5-10 minutes. Peripheral branch used for cannulation can be embolised to prevent post-surgery bleeding. After the transplantation it is necessary to continue in the insulin therapy, to prevent the new islets from destruction with high glucose levels. Pacients are similarly to the organ transplantation treated with immunosuppression.[1]

Future

Given the lack of donors the organ transplantation will probably not become widely used method of treatment of diabetes. Only in the Czech Republic every year about 25 pancreases are taken. According to gueses it would be possible to get about 40 pancreases for the islets isolation per year. This amount is needed for transplantation to 10-15 pacients. Some hopes are given to transplantaitons of animal islets of Langerhans or geneticaly modified insulin producing cells with induced im0unological tolerance. Thanks to that, this form 6f treatment could be used in treating type 2 diabetes as well.[1]

Alternative sources

These days it is theoreticaly possible to consider only the pig tissue or the development of proper genetically modified insulin producing cell lines. If we look away from the uncertain risk of transmition of pig's endogenous retroviruses, the immunological barrier is still higher in the xenogeneic tissue than in the allogeneic. Modified cell lines have to meet many criteria:

- effective growth with a possibility of a following inhibition
- sufficient insulin production
- controled insulin secretion dependent on the organism's needs
- low or none immunogenicity

To consideration there are geneticaly modified insular or noninsular cells, transformed B-cell lines, embryonic stem cells, tissue specific stem cells. On the animal models there was succesfully described the differentiation technique of the stem cells in the cells resembling the pancreatic B-cells, which reacted to the glucose levels by producing insulin. In humans, a life-long diversification in the B-cells was proven. Gradually, a line of signal genes and their products was discovered, which control the differentiation of the tissue-specific stem cells. The knowledge of differential mechanisms or the artificial modification of cells could lay the basics of a mass production of the B-cells as an alternative source of insulin producing tissue.[1]

BioHub

BioHub is a bioingeneeting project DRI (Diabetes Research Institute), which has a goal to imitate fysiological pancreas function. It is a miniature machine implanted inside a body between the omental layers, including insulin producing cells, which are able to react to the glucose level in the blood steam and dissolve only the needed amount of insulin. Some pacients can profite for decades. As opposed to the islets transplantation this method has a higher universality: destructions by the immune system should not occur; better oxygenation of the cells inside the BioHub until there are its own vessels produced; better nutrition of the cells. BioHub is trying as faithfully as possible to imitate fysiological environment of the pancreas. It also gives another oportunity of oxygenation or the helper cells, which improve long-term vitality of the insulin producing cells, lower the inflame reaction and the unwanted immune reaction. BioHub itself can be inhabited by other cell types. There is a possibility of application of immunosuppressives locally directly into the preparate – that way it does not have a systemic effect.[3] [4]

Links

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Source

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4. https://www.diabetesresearch.org/biohub

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