

Is Islet Transplantation an alternative to Simultaneous Pancreas - Kidney Transplantation?

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Background

- **Problem of Diabetes**

„Diabetes mellitus, the metabolic disorder is **rapidly on the rise**, becoming one of the main threats to human health and imposing large socio-economic burden on the society in the 21st century...” (Dall et al.; 2010).

International Diabetes Federation in 2011 estimated that over 300 million people around the world have diabetes and is expected to **rise to 500 million within next 20 years**.

Diabetes is a leading cause of premature illness and death worldwide!

Why should we talk about diabetes in a Nephrology School?

According to the **American Diabetes Association**:

Diabetic nephropathy accounts for **40%** of newly diagnosed cases of **end-stage renal disease** in the USA

It's seen in **20-30%** cases of **type-1 or 2 diabetics** – greater proportion of those with type-1

Nota bene!

A knowledge that may someday help you....



Background – DM – pancreas tx

- **Definition:**

1. Diabetes mellitus type 1 is an autoimmune disease with antibodies against islet cell antigens (GAD, ICA, IA-2)

- onset in childhood and youth
- destruction of all islet cells, there is no insulin secretion

2. Type 2 diabetics show preserved or even increased insulin secretion with underlying peripheral insulin resistance

- pancreas tx performed sporadically in type 2 DM, this is not yet accepted to be a proven indication

Background – Type 1 DM

- **Two treatments:**

- 1. Exogenous insulin administration**

- burdensome to the patient (QOL)
- gives imperfect glycaemic control
- predisposing to secondary complications (eyes, nerves, kidneys, etc.)

- 2. β -cell replacement by pancreas or islet transplantation**

- when successful, establishes a constant euglycemic state
- **BUT** (whole pancreas tx) requires major surgery...
- ...and immunosuppression to prevent rejection

Background – Pancreas Tx

- **Pancreas transplantation can....**

- restore the production of endogenous insulin
- help in the counterregulation of glucose metabolism
- avoid hyperglycemia and hypoglycemia episodes

- **Patient rendered insulin-free through a pancreas tx**

- improvement in QOL
- reduction as well as reversal of some microvascular complications
- elimination of the process of daily insulin injections and frequent glucose monitoring

Background – Pancreas Tx

- **In the long term...**

- stabilizes retinopathy
- improves neuropathy
- causes regression of nephropathy by improving glomerular architecture, reverses interstitial expansion, resorpts atrophic tubules
- improves macrovascular disease, cardiac function and endothelial function

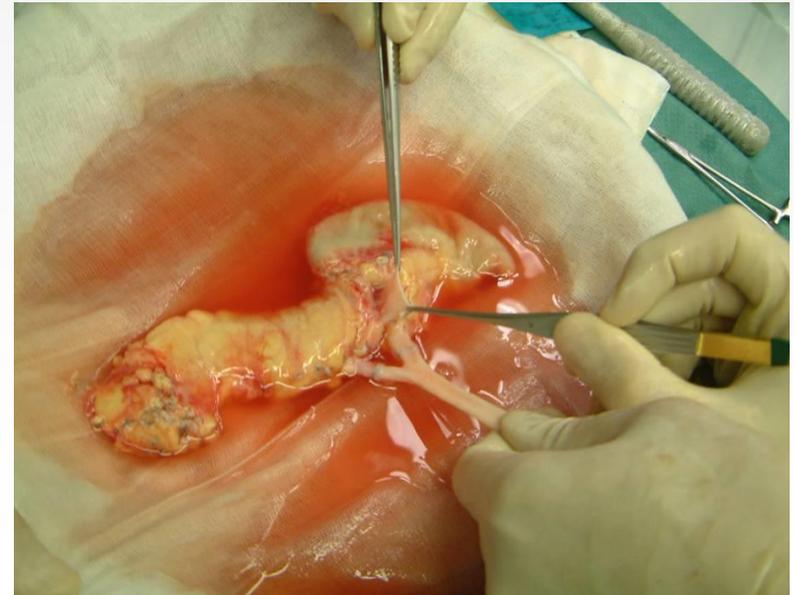
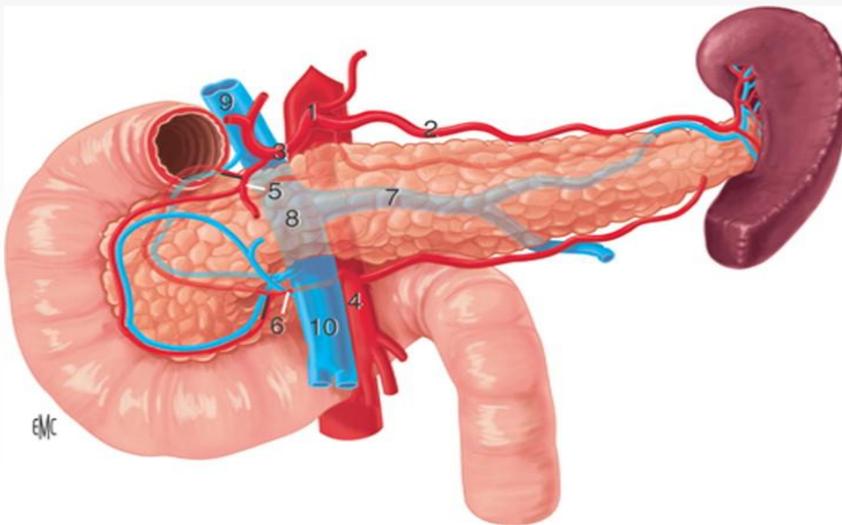
- **However there is no improvement in advanced vascular disease and retinopathy....**

Advantages are greater if it is done before the onset of severe complications!

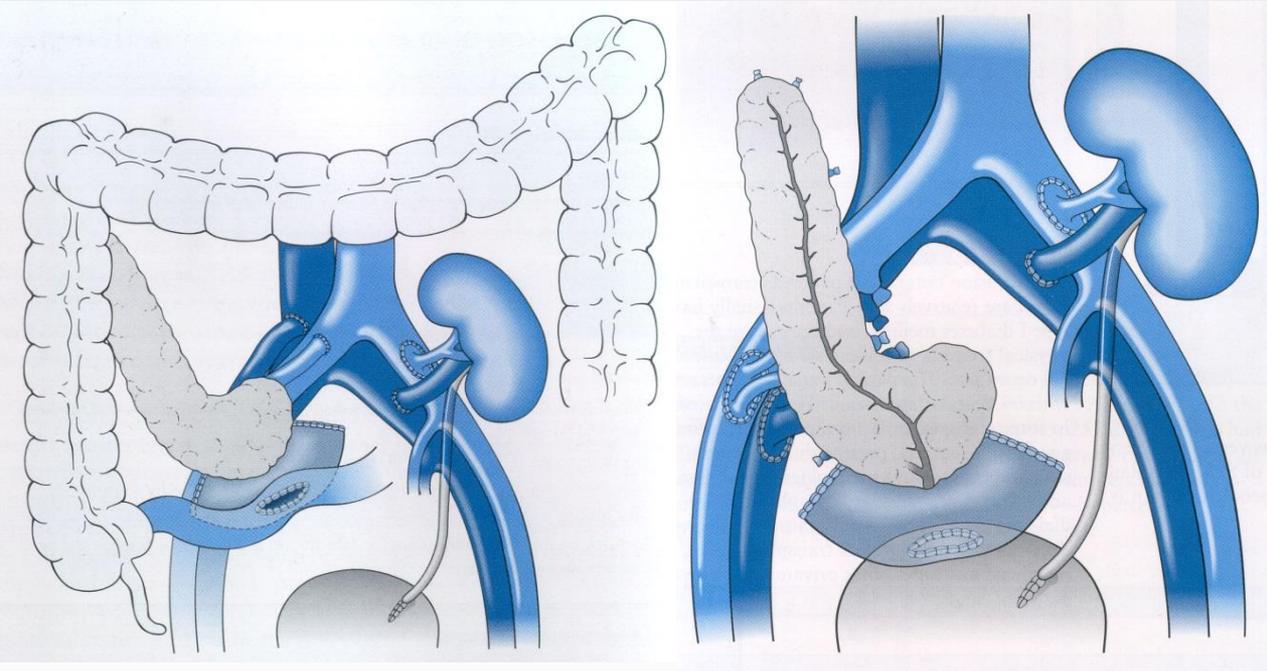
Background – Pancreas Tx

■ Surgical technical options:

- arterial anastomosis with donor iliac Y-graft or aortic patch of CT and SMA
- portal venous anastomosis:
 1. systemic – venous (vena cava)
 2. portal – venous (branch of mesenteric vein)
- exocrine drainage
 1. enteric (small bowel or duodenum)
 2. bladder

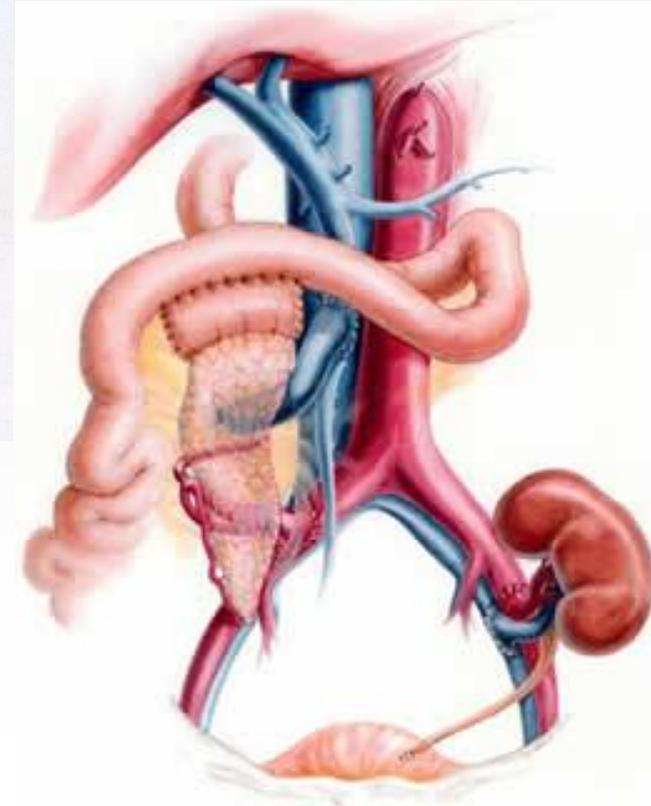


Background – Pancreas Tx



Systemic-venous drainage with enteric (left) and bladder drainage (right)

Portal-venous drainage with enteric drainage



Whole pancreas transplantation



Surgery

Immuno-
suppression

Most of the surgical complications are related to the exocrine part of the organ! They are still frequent and may result in relaparatomy!

BUT

The most common cause of whole pancreas allograft failure in the first week after transplantation is the **graft thrombosis!!!**

Bleeding

Graft thrombosis

Pancreatic leak

Pancreatitis

Acidosis, dehydration

Rejection

Infection

Malignancy



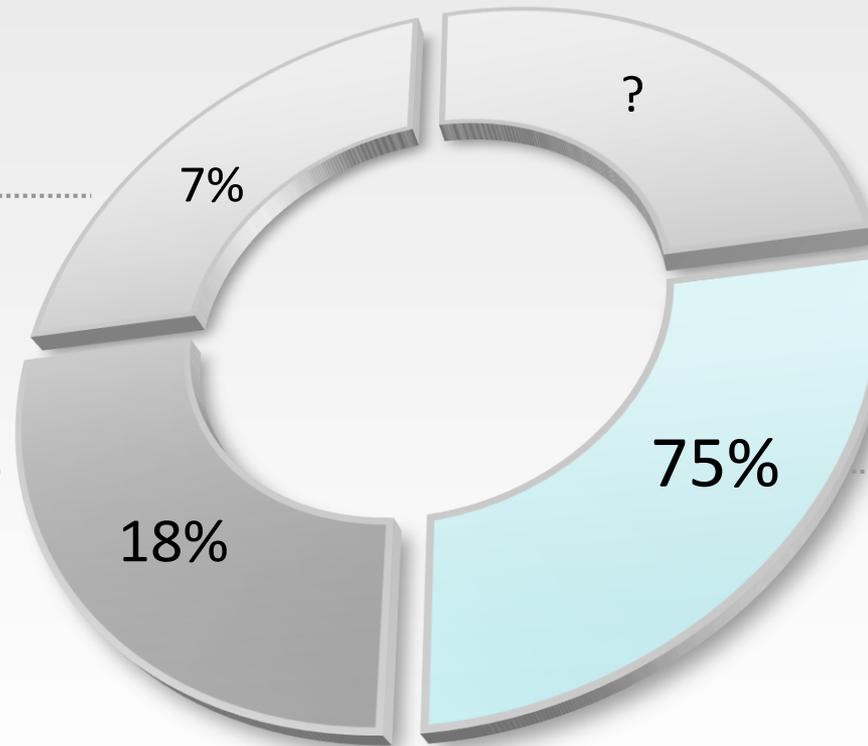
Background – Pancreas Tx

- **Indications of pancreas tx**

- **Simultaneous pancreas kidney tx (SPK)** is considered to be a life-saving therapy for type-1 diabetics with concomittant end-stage kidney disease
- **Pancreas after kidney tx (PAK)** is performed in lower numbers
- Regarding the excellent results of living kidney tx (LDK), **pancreas transplantation after LDK (PALK)** offers the advantages of a living donor kidney with **shorter duration of dialysis** and a **functional pancreas**
- **Pancreas transplantation alone (PTA)**, prior to presence of diabetic nephropathy, is performed very rarely and is indicated only for patients with severe problems in managing their diabetes (e.g. hypoglycemic unawareness)

Background – Pancreas Tx

PTA (Pancreas tx
alone)



Islet tx ??

PAK (Pancreas
after kidney tx)

SPK
(Simultaneous
pancreas kidney
tx)



Islet transplantation

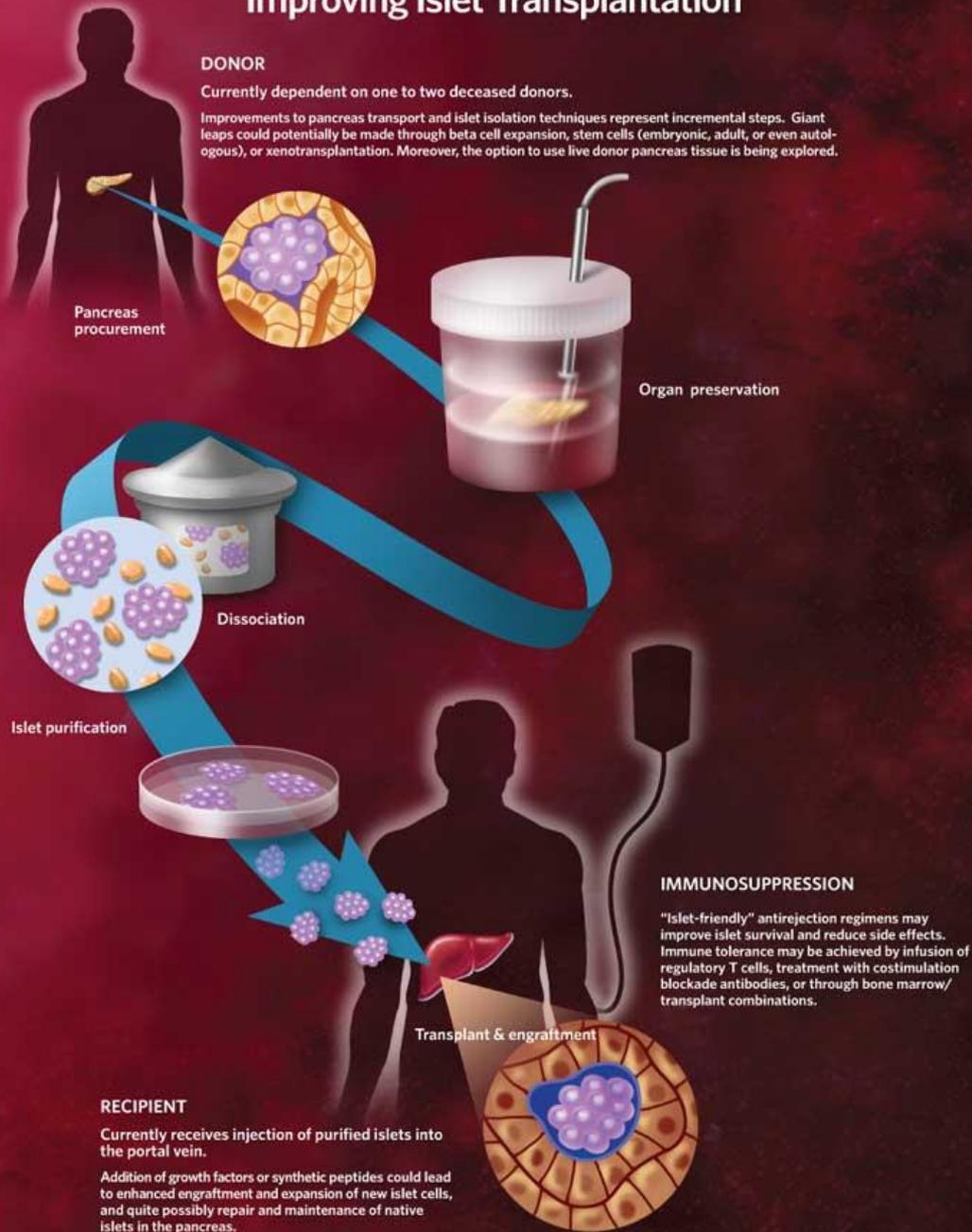
- **Another type of β -cell replacement using deceased donors**

- **Donor criterias: over age 50 with BMI>30** (opposite whole pancreas donors)
- extraction of islet cells from the pancreas by **enzymatic digestion** of the parenchyma, and subsequent **purification**
- the islet cells are then **injected into the portal vein** of the recipient (by radiological or surgical approach)

- **Indications**

- C-peptide negative patients with severe glycemic lability, recurrent hypoglycemic episodes and a reduced ability to detect the symptoms of hypoglycemia (**ITA = islet tx alone**)
- alternative for type 1 diabetics with ESRD? (**IAK = islet after kidney tx**)

Improving Islet Transplantation



Islet tx...

...involves:

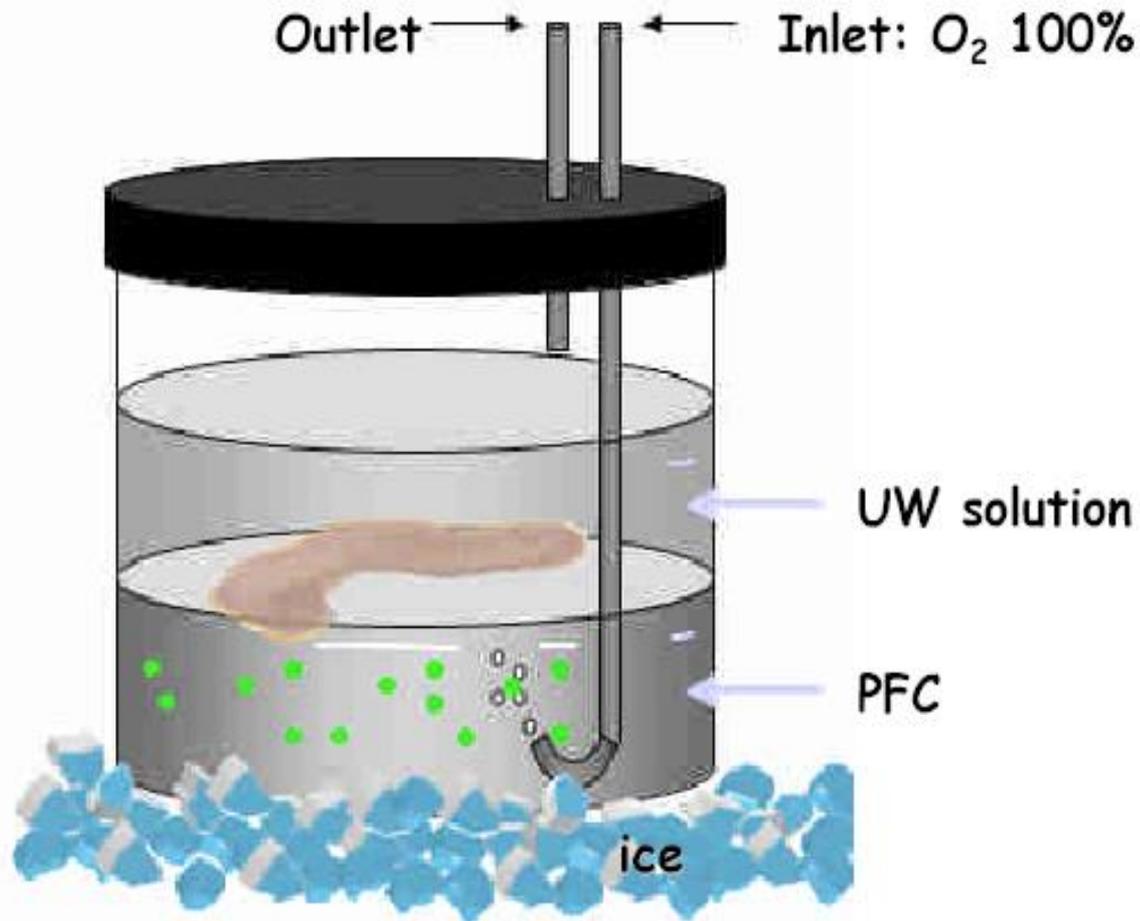
- procurement of a donor pancreas
- subsequent digestion and separation of the exocrine tissue and stroma from the islets (enzyme degradation and density centrifugation)
- isolated islets are assessed for quantity and quality
- Islet preparations that contain an adequate number of islets (5000 IEQ/recipient kg) are then transplanted into a diabetic recipient

Islet transplantation



Pancreas procurement

Islet transplantation



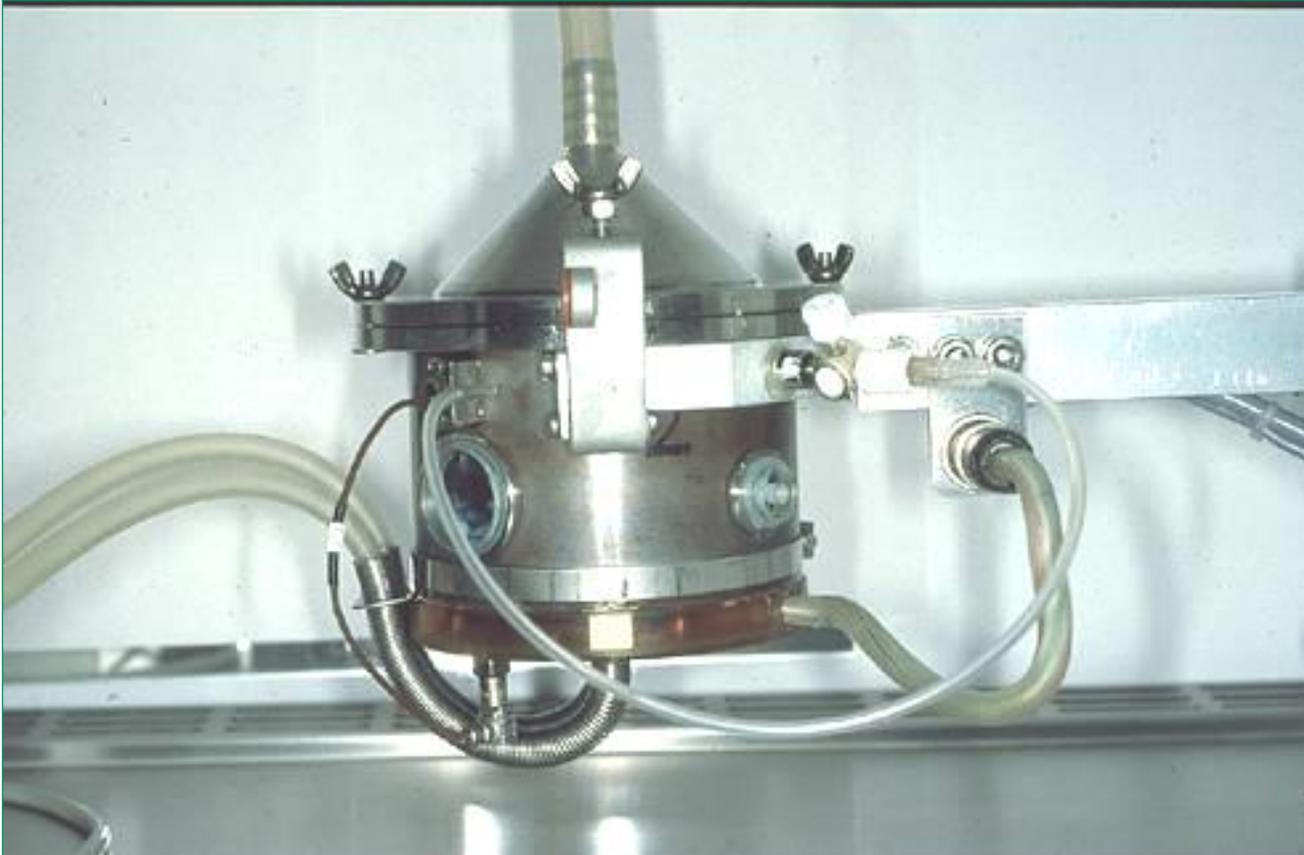
Transport – double layer

Islet transplantation



Cannulae are inserted – solution containing class I and II collagenase and neutral protease thermolysin → then cut into several pieces

Islet transplantation



Enzymatic and mechanical processing – Ricordi-chamber

Islet transplantation

After enzyme wash-out and tissue collection – purifying and separation by density gradient

Quantification and quality assessment



Islet transplantation

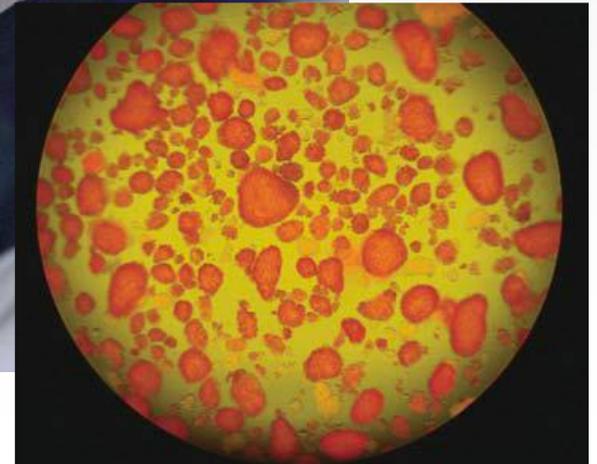


Pre-transplant „overnight” culture

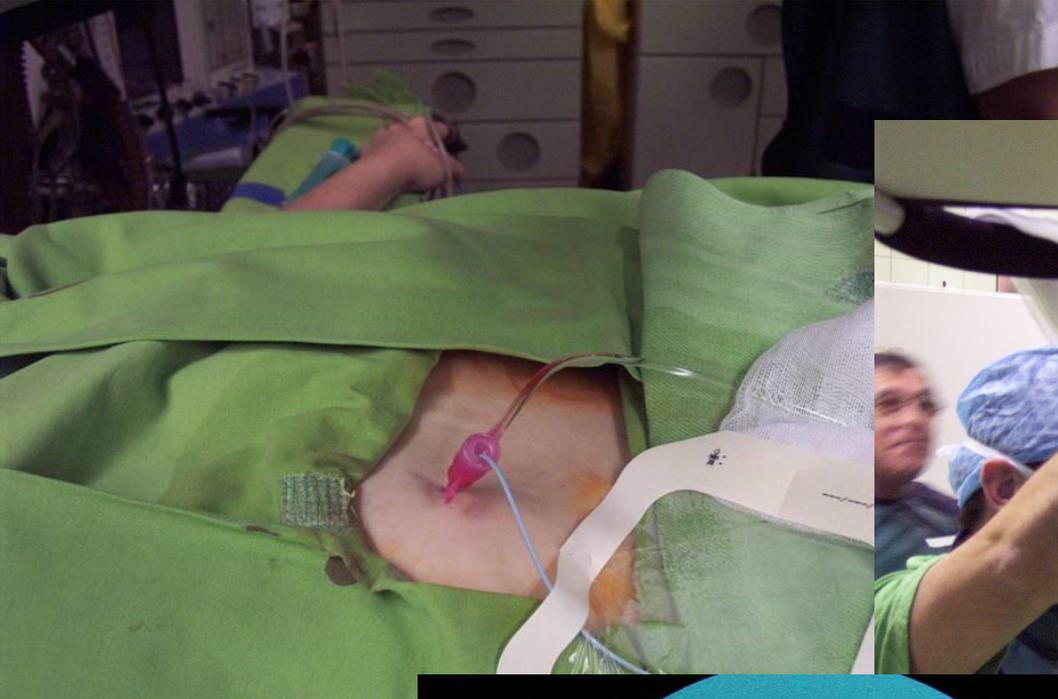
Islet transplantation



Islet infusion



Islet transplantation



Transplantation process

Islet transplantation

▪ Advantages

- **No need for major surgical procedure!**
- Long-term conservation is possible
- Severe complications are rare (bleeding, portal thrombosis)

▪ Disadvantages

- islets are at least as prone to immunological rejection as the whole organ..
- ...and even more sensitive to the autoimmune milieu typical for type 1 DM
- Activation of the coagulation and inflammatory pathways following intravascular infusion of islets (**IBMIR** = instant blood-mediated inflammatory reaction)
- all of these led to graft loss → **Islet count from one pancreas is usually insufficient**



Islet transplantation

- **The „Edmonton Protocol” (Shapiro et al. 2000)**

- series of seven patients with T1DM receiving islets from multiple (2–4) donors, **100% of recipients achieved insulin independence! (82% at 1y)**
- proposed the use of a **steroid-free immunosuppression** protocol based on:

Tacrolimus (CNI),

Sirolimus (mTOR inhibitor),

Anti-CD25-receptor (IL-2) antibody (e.g. daclizumab)

transplantation of a larger islet mass (>11,000 IEQ/kg recipient weight) and

avoidance of islet culture before transplantation.



(Although islets are now routinely cultured, steroids continue to be avoided in posttransplant immunosuppression regimens. The use of multiple donors, while enabling the transplantation of a large islet mass, limits the number of patients that can receive grafts.)

Islet transplantation

▪ Recent outcomes

- The Edmonton group and others have observed an inexorable decline in insulin independence out to 8 yr posttransplant, but with persistent C-peptide secretion and complete protection from hypoglycemic reactions in >70% of recipients
- **In the most recent era** shift to **introduction with a T-cell depleting antibody**, with or without an **inhibitor of tumor necrosis factor- α** (TNF- α ; e.g., etanercept) and **maintenance with an mTOR inhibitor or an inosine monophosphate dehydrogenase inhibitor** (e.g., mycophenolic acid) combined with a **CNI**.
- There were also definite shifts in **preservation** method and **collagenase** type, and more islet preparations were **cultured**.

Islet transplantation

- **Recent outcomes**

The **Collaborative Islet Transplant Registry (CITR)** report showed improved islet graft survival rates:

Insulin independence at 3 years after islet transplantation improved from 27% in the early era (1999–2002) to 37% in the mid (2003–2006) and to 44% in the most recent era (2007–2010)”



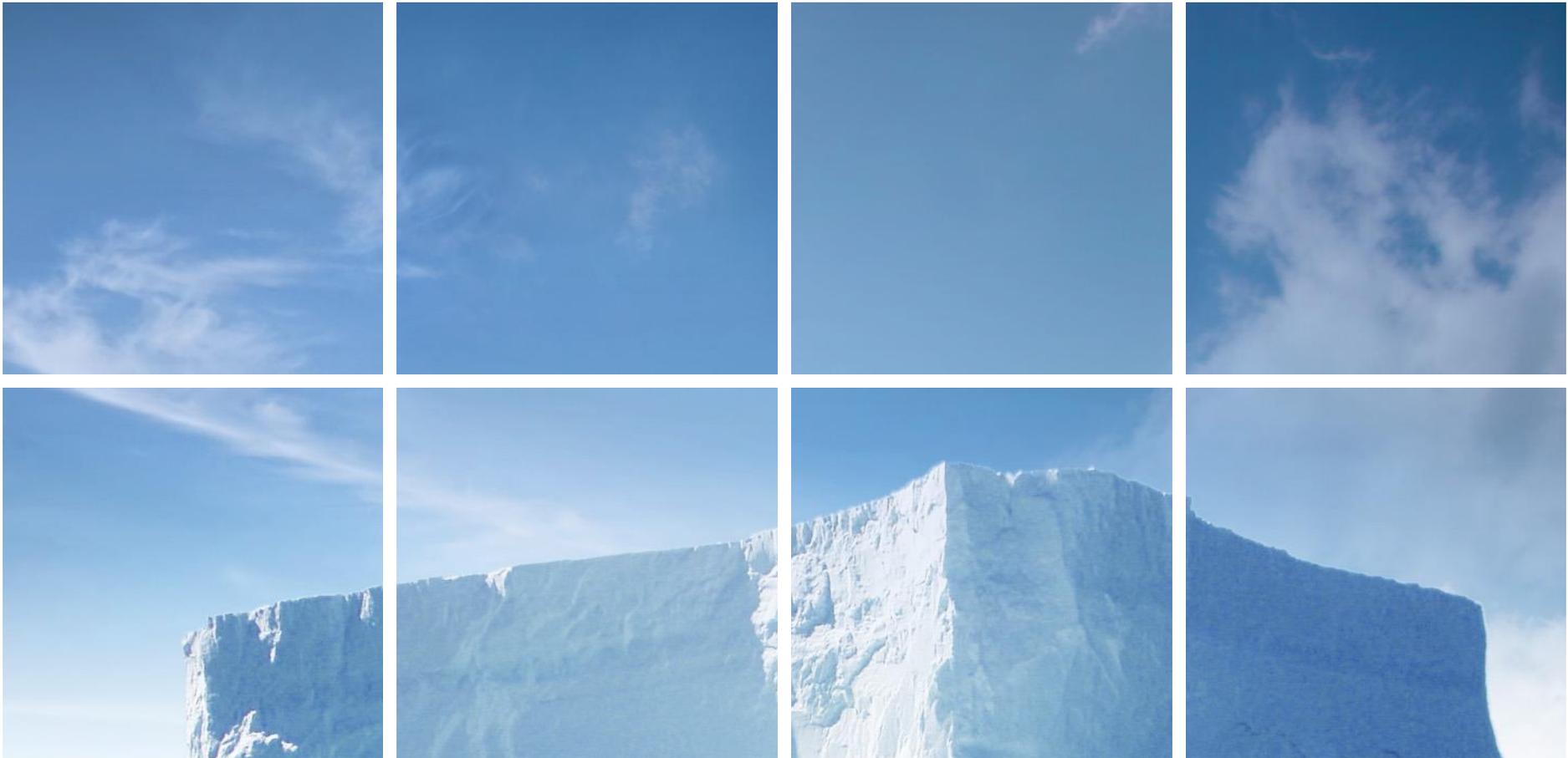
Conclusions

Islet transplantation currently offers substantial protection from severe hypoglycemic episodes and high rates of freedom from exogenous insulin requirements in a minimally invasive setting.

Whole pancreas transplantation is an approved option for β -cell replacement in type 1 diabetes, although it is mostly limited to patients simultaneously receiving a kidney transplant for diabetic nephropathy (**SPK**) and often excludes older patients and those with coronary artery disease due to the potential for significant surgical morbidity.

Thus, islet transplantation may offer a complementary alternative to whole pancreas transplantation in patients who are not candidates for or are unwilling to accept the risks of major surgery, and so some estimation of comparative efficacy is required.

Emerging innovations in islet production, processing, delivery, and immunosuppressive protection undoubtedly will advance the field.



Thank you for your attention!

