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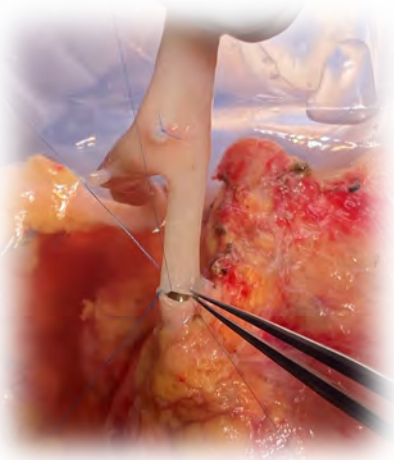

Simultaneous Kidney Pancreas and Islet Transplantation

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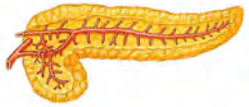
No disclosure

Outline

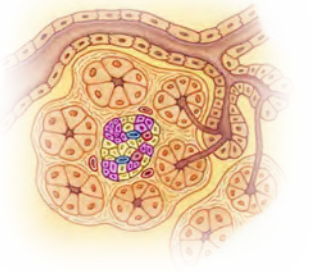
- Background: Diabetes Epidemiology and current indications
- Brief description surgical technique
- Short and long term outcomes after SPK
- Islet transplantation

Surgical Therapies for Beta cell replacement

Pancreas (solid organ)

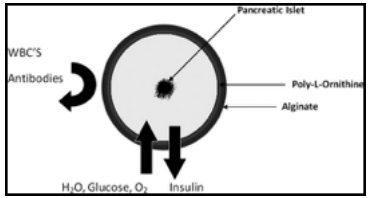


Islets (allograft)



Stem-cell derived islets

Microencapsulated Islets



Xenografts

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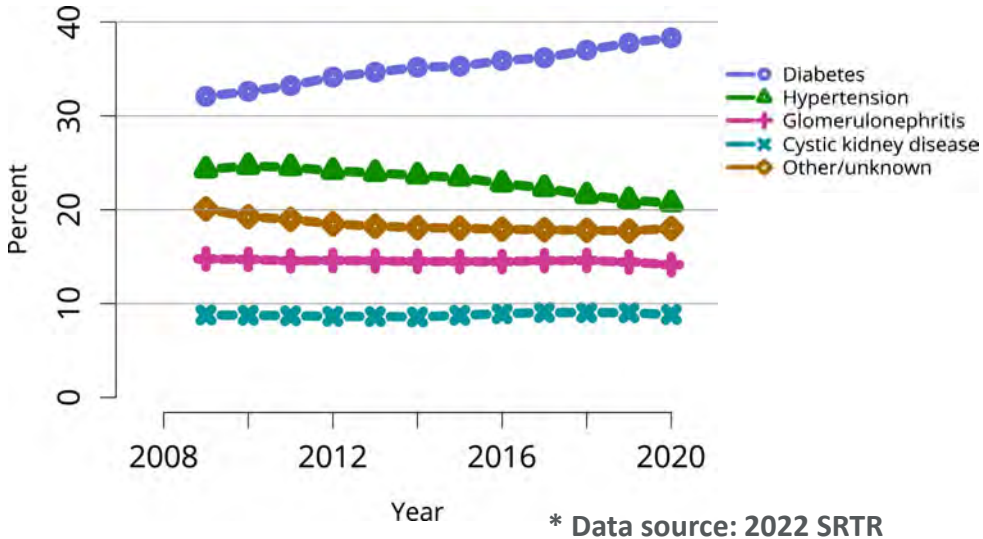
Background

Diabetes Mellitus

Epidemiology in United States

- **Prevalence:**
  - ~ 29.1 million (9.3%)
  - 95% Diabetes mellitus type 2
- **Incidence:**
  - 1.7 million (annually)
- **Most common cause CKD (~44%)**
- Number of pancreas transplant performed:
  - 3 per 10,000 patients with type I
  - 3 per million patients with type 2

Etiology CKD (Waiting list) *



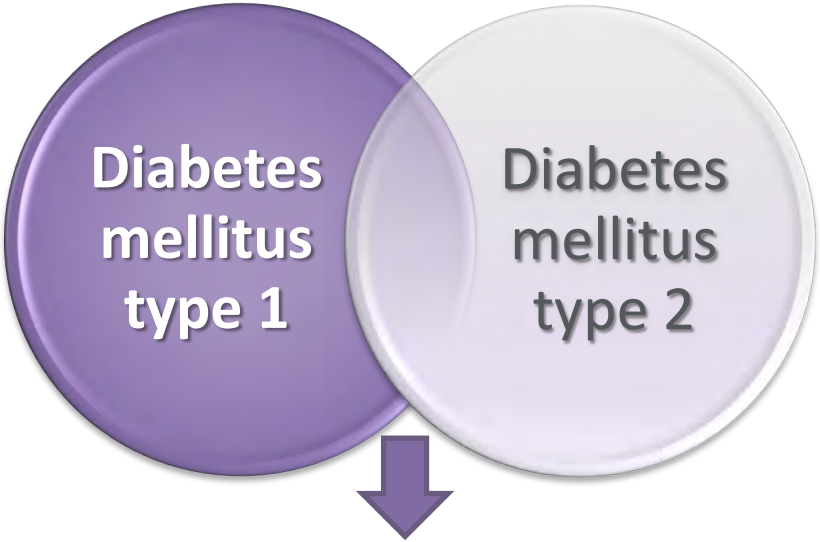
*** Data source: 2022 SRTR**

Current Transplant Rep 2015 ; 2 : 149 - 158
Am J Transpl 2022 ; 22 : Issue S2 : 21 – 136.

Pancreas Transplant Indicated

Pancreas Transplant Contraindicated

Autoimmune
Insulin deficiency
(C-Peptide)
BMI usually low
Younger



Insulin Resistance
Overweight / obesity
Immunosupression

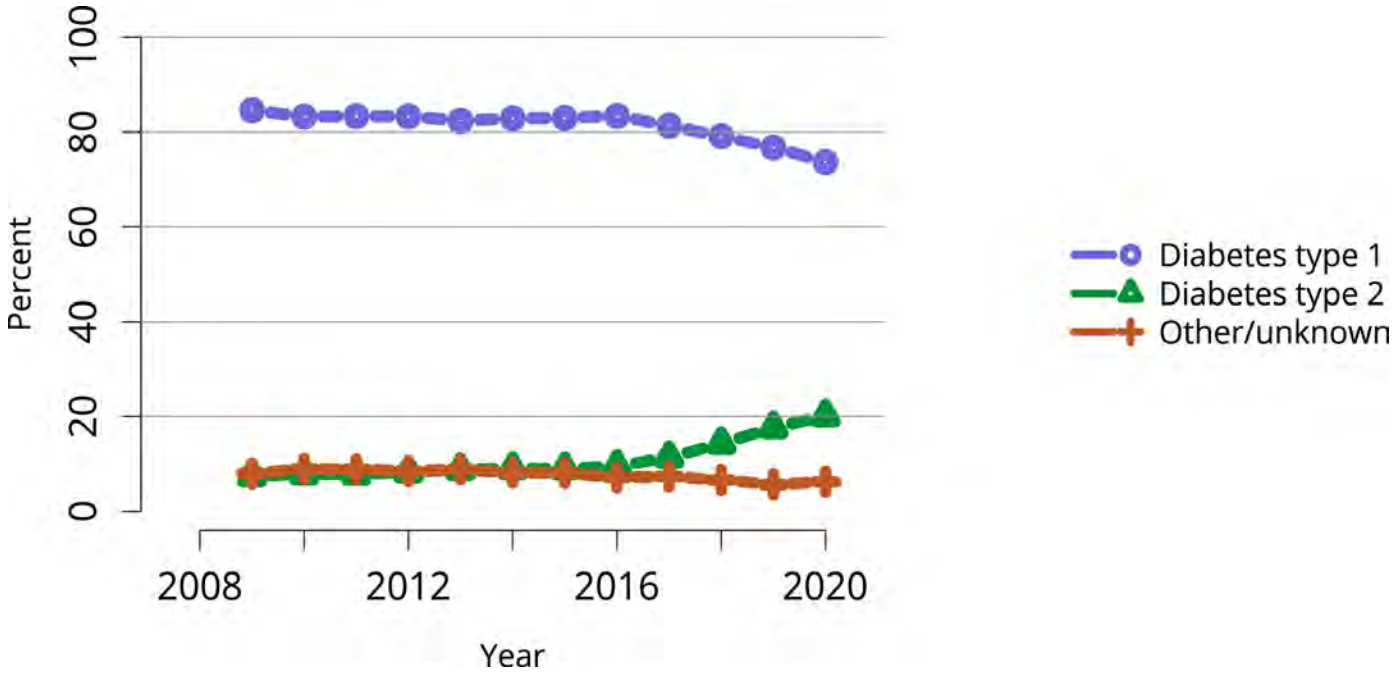
93%

7 %

Age < 55 – 60 years
No evidence insulin resistance
BMI < 30 – 32 kg / m^2
C-Peptide < 10 ng/ml
Insulin at least 3 to 5 years

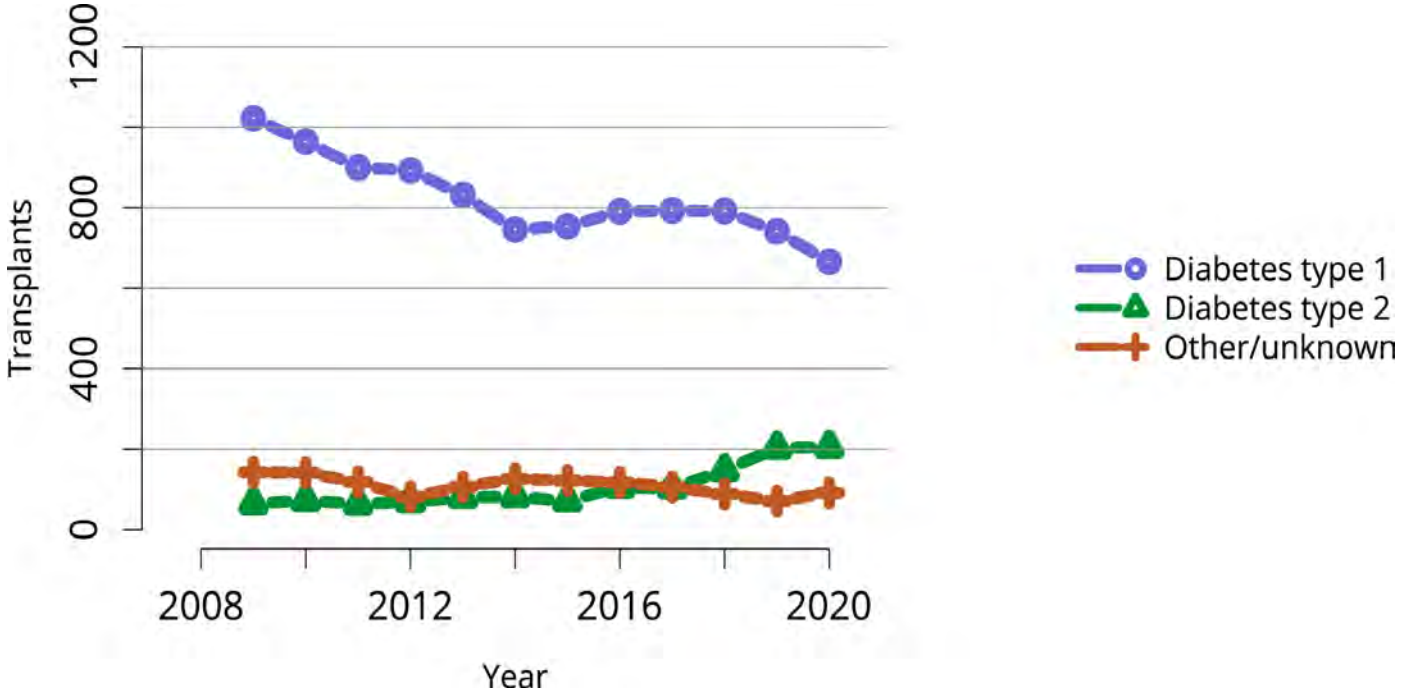
Adults waiting for pancreas transplant by diagnosis

Data source: 2022 SRTR



Pancreata transplanted in United States

Date source: 2022



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Indications for transplant

Who should be referred for a pancreas transplant?

1. **Diabetes Mellitus type 1 and CKD Stage 4 or 5**
2. **Diabetes Mellitus type 2 and CKD Stage 4 or 5**
   - No evidence of insulin resistance (less than 100 or 1 unit / kg)
   - Age < 55 – 60 years
   - C peptide < 10 ng/ml
   - No cardiopulmonary complications
   - BMI < 30 – 32 kg / m^2
   - Insulin for at least 3 years
3. **Previous kidney transplant recipient + DM type 1 or 2**
4. **Other medical complications**

Curr Transpl Rep 2015 ; 2 : 149 – 158.

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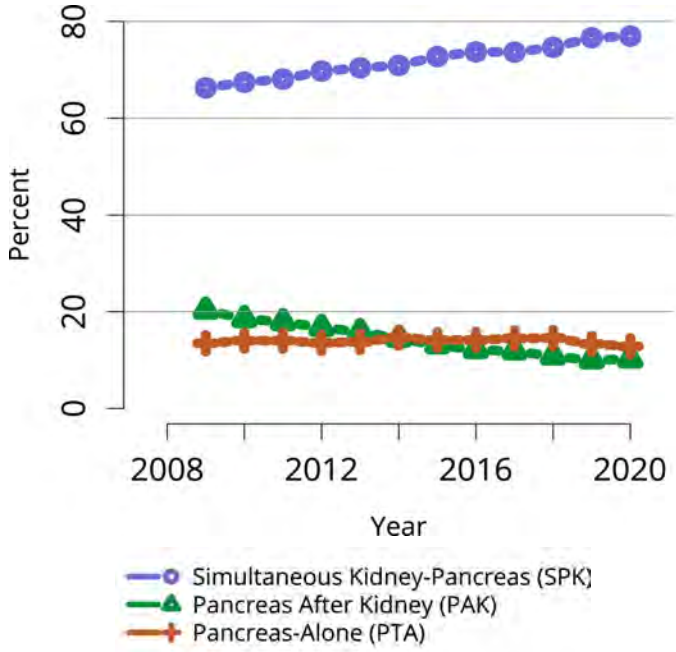
Current SPK Transplant Indications

Diabetes Mellitus

Adults waiting for pancreas transplant



Nat Rev Endocrinol 2013 ; 9 : 555 – 562.
Am J Transplant 2022 ; 22 : Issue S2.

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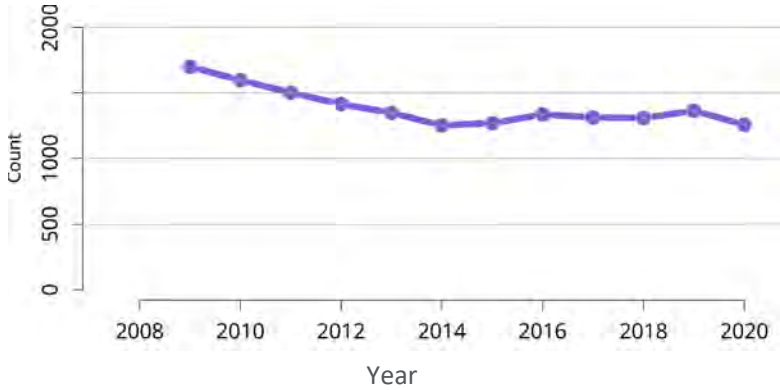
Challenges pancreas transplant

Why not more cases?

- Diabetes Mellitus control has improved
- Risk / benefit associated with immunosuppression:
  - Opportunistic infections
  - Risk of cancer
- Organ shortage / decreased quality
- Operation considered “Technically difficult”
- Frequently considered **“Non Life-Saving Organ”**

Pancreata recovered for transplant in the US



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Pre-Transplant Evaluation

Multidisciplinary team

Absolute contraindications

- Uncontrolled infection
- Active cancer
- Severe CAD
- Major PVD – iliac vessels
- Active addictions
- Poorly controlled psychiatric diseases
- Poor social support
- Other **

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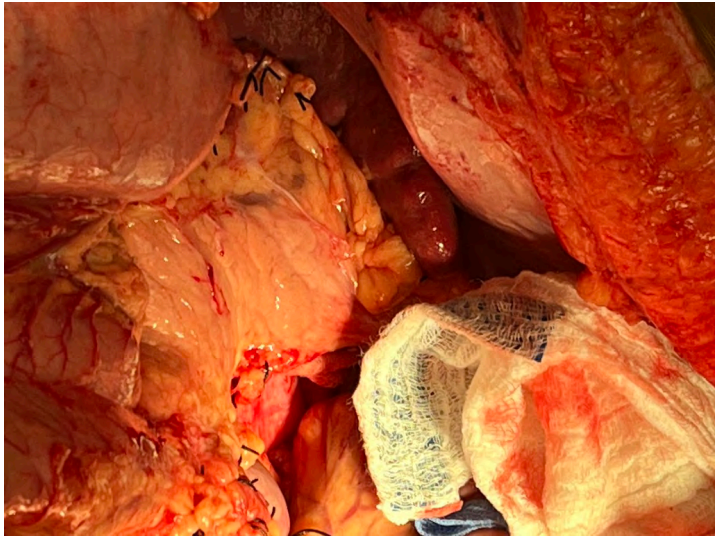
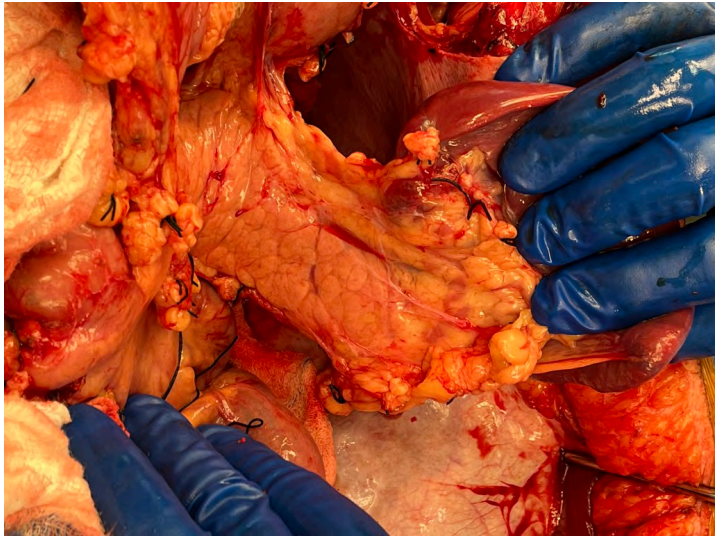
Surgical technique Indications for transplant

Three major surgical components

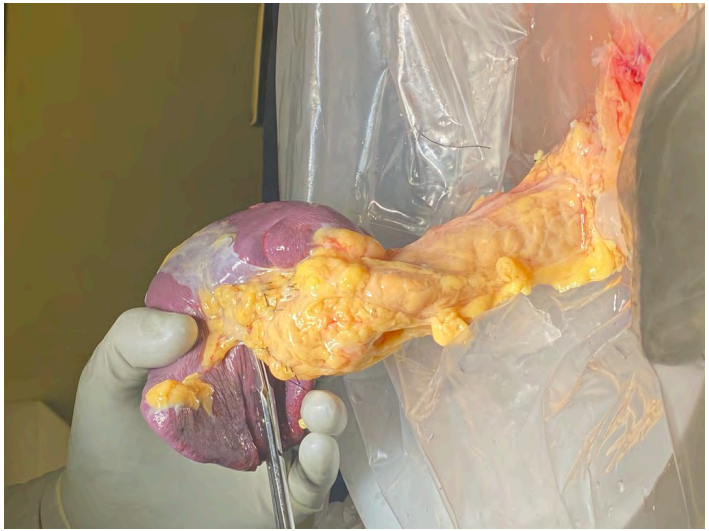
1. Pancreas procurement
2. Backbench preparation of the pancreas graft
3. Transplant into recipient

Pancreas procurement

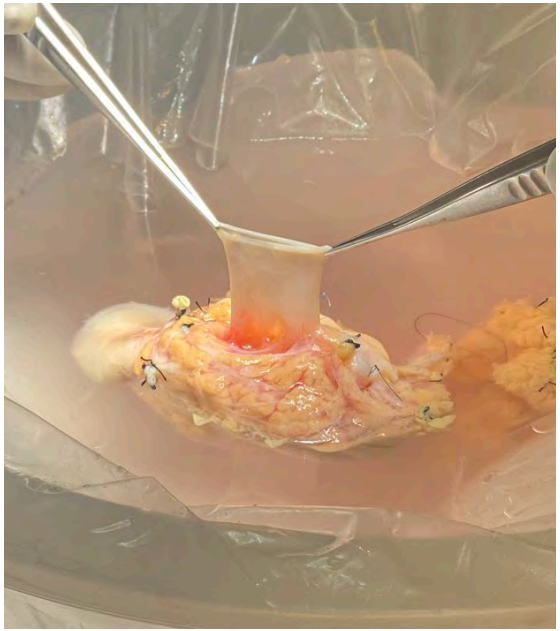




Backbench preparation of pancreas graft

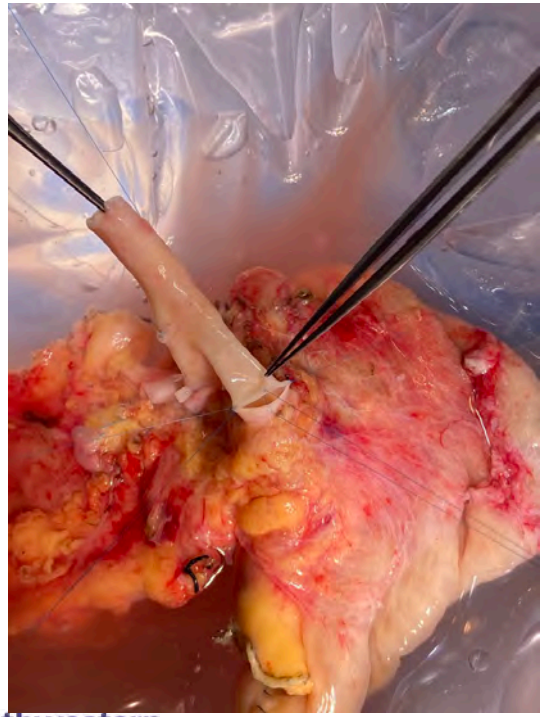


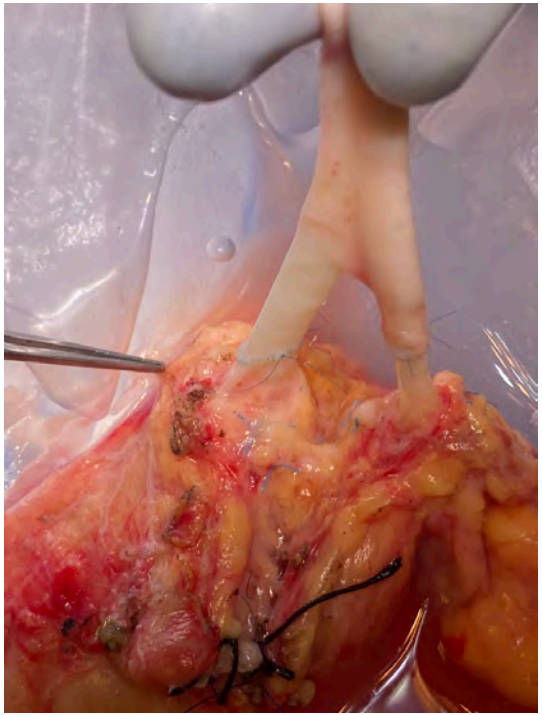
Backbench preparation of pancreas graft



Backbench preparation of pancreas graft

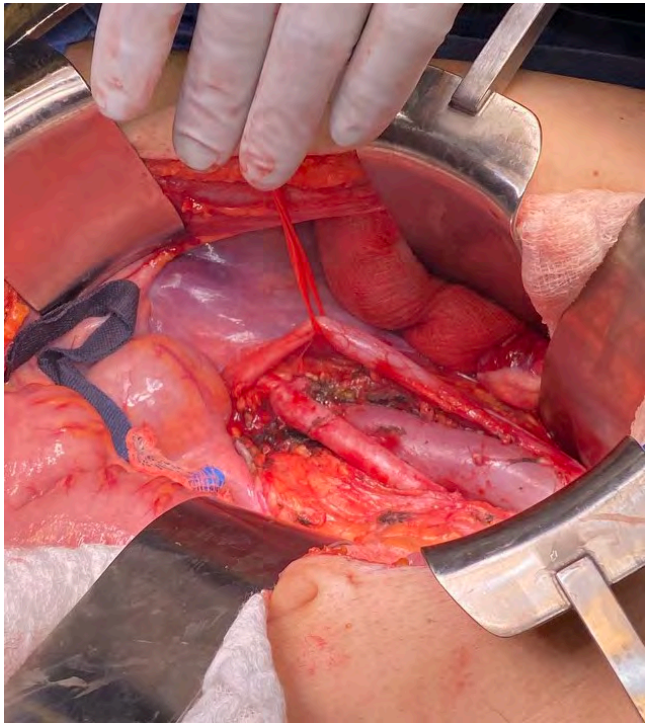
Creation of the Y – Graft

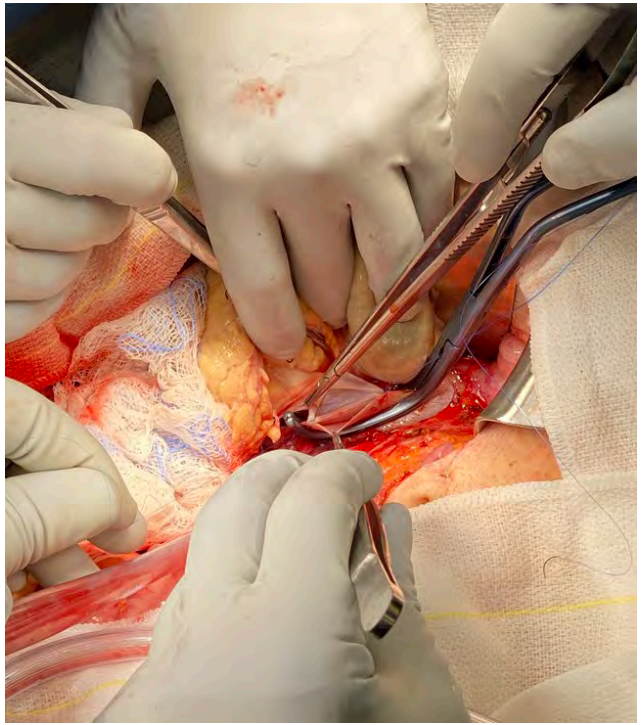




Transplant in Recipient

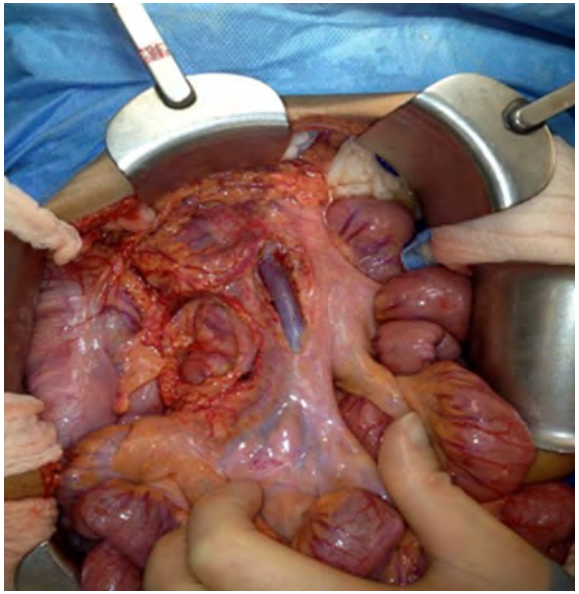
Systemic drainage

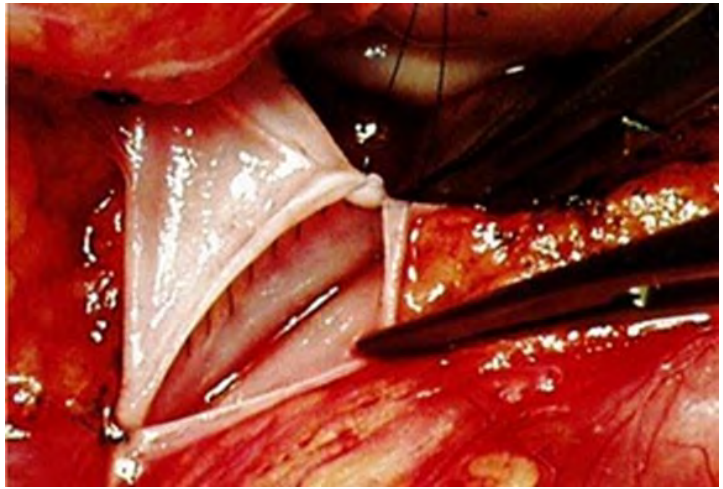




Transplant in Recipient

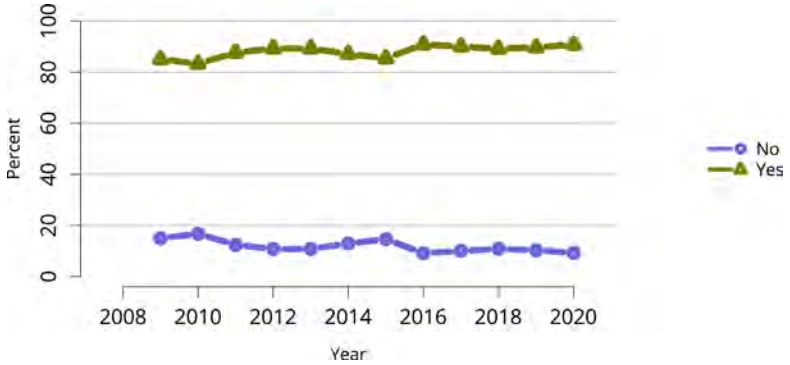
Portal drainage



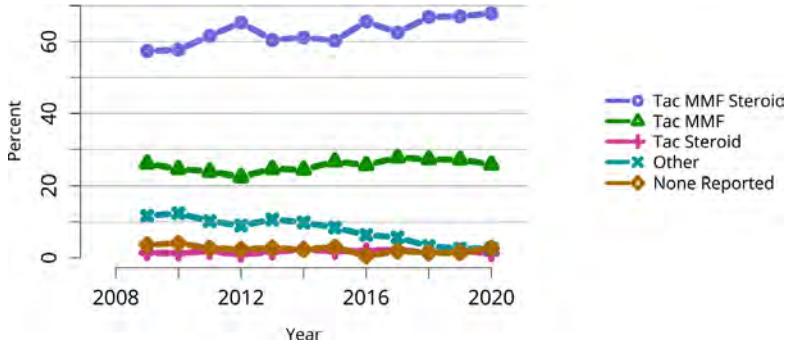


Immunosuppression

Induction



Maintenance



Immunosuppression at NMH

- Induction: Alemtuzumab / Methylprednisolone
- Maintenance: MMF + Tacrolimus

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Outcomes after transplant

Patient survival

Data source: International Pancreas Transplant Registry

Type of transplant	1 – year survival	3 – year survival
SPK	97.6%	94.6%
PAK	97.2%	92.9%
PTA	97.9%	95.5%

Cause of death:

0 – 3 months: Infections, CVA
4 – 12 months: Infections
2 – 5 years: CVA, neoplasms (7%)

- **Risk factors for patient death ***
  - Age > 45 : 1.65 (< 30 in PTA)
  - Dialysis prior transplant 1.38
  - Pancreas status : 2.56
  - Kidney status : 10.38
  - Type of kidney donor **
    - DDKT : 1.46

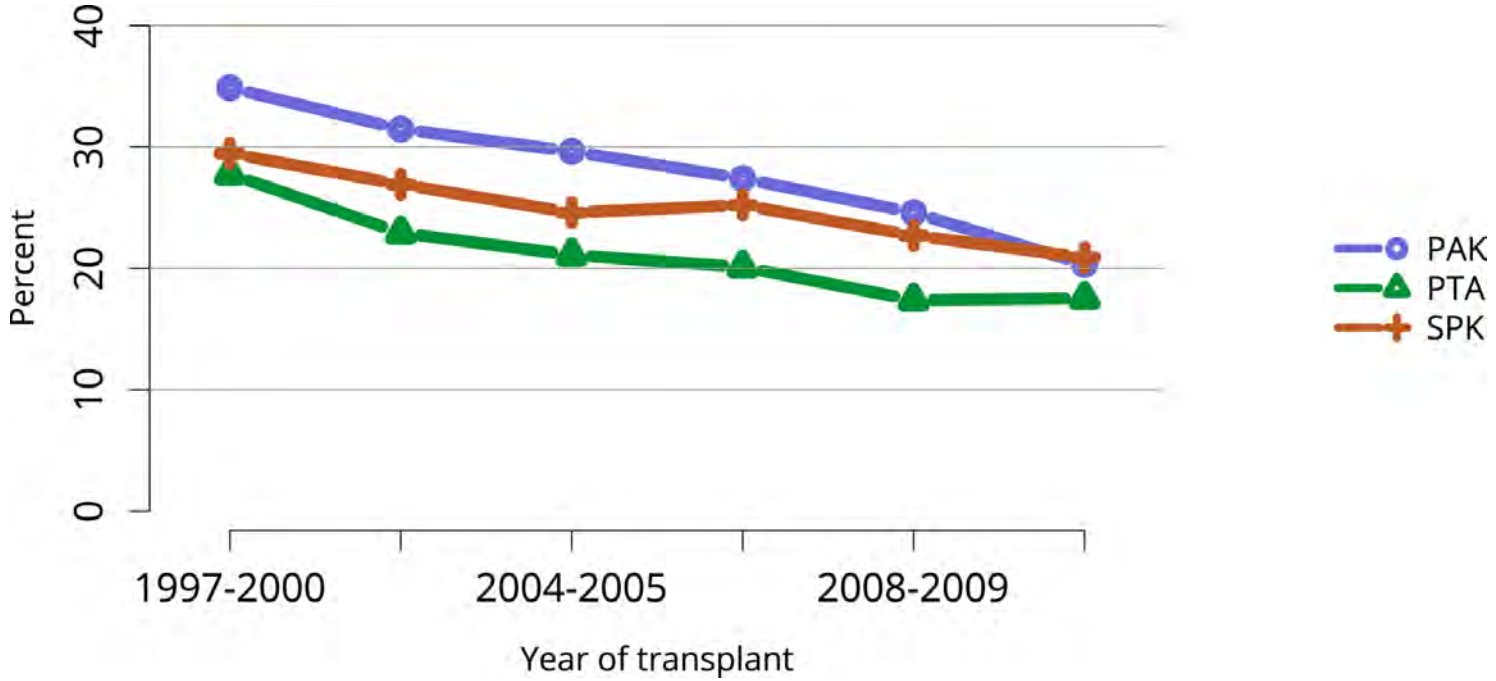
*** Race, gender, type of DM do not influence**

**** Only for PAK**

Gastroenterol Clin N Am 2018 ; 47 : 417-441.

Patient death at 10 – years after pancreas transplant

Data source: 2022 SRTR



Am J Transplant 2022; ; 22 : Issue S2.

Pancreas (Graft) function

International Pancreas Transplant Registry

Type of transplant	1 – year graft function	3 – year graft function
SPK - Pancreas	89.9%	83.4%
SPK - Kidney	95.7%	89.5%
PAK	88.5%	74.4%
PTA	83.9%	71.4%

- **Causes for graft loss:**

0 - 3 months:	Technical failure
	Patient death
4 – 12 months:	Patient death
	Immunologic
	Infections
> 1 year:	Immunologic
	Patient death

Gastroenterol Clin N Am 2018 ; 47 : 417-441.

Pancreas (Graft) function

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    Immunologic
    Infections
  - > 1 year: Immunologic
    Patient death

Gastroenterol Clin N Am 2018 ; 47 : 417-441.

Technical failure

International Pancreas Transplant Registry 2011 - 2016

Technical failure	SPK	PAK	PTA
Thrombosis	4.2	4.4	4.9
Infection	0.3	0.3	0.2
Pancreatitis	0.2	0.2	0.2
Anastomotic leak	0.4	0.2	0.2
Bleeding	0.1	0.2	0.2
Other	0.4	0.4	0.4
TOTAL	5.6	5.7	6.1

Gastroenterol Clin N Am 2018 ; 47 : 417-441.

Technical failure

International Pancreas Transplant Registry 2011 - 2016

Technical failure	SPK	PAK	PTA
Thrombosis	**4.2**	**4.4**	**4.9**
Infection	0.3	0.3	0.2
Pancreatitis	0.2	0.2	0.2
Anastomotic leak	0.4	0.2	0.2
Bleeding	0.1	0.2	0.2
Other	0.4	0.4	0.4
TOTAL	5.6	5.7	6.1

Gastroenterol Clin N Am 2018 ; 47 : 417-441.

Technical failure

Graft thrombosis

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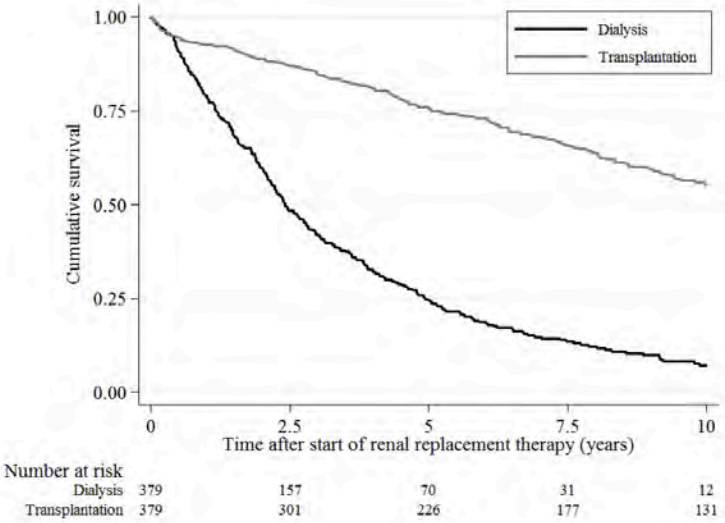
Effect on long term complications

Long term outcomes

Netherlands (1986 – 2016)

- 2,796 patients with type 1 diabetes requiring RRT
  - 996 transplanted
  - 1,800 dialysis

Patient survival after RRT
(Dialysis or kidney transplantation)



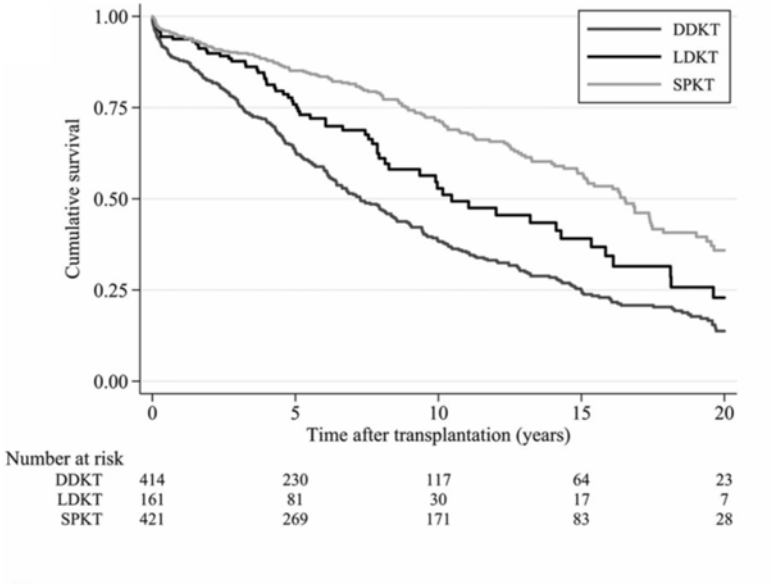
Diabetes Care 2020 ; 43 : 321 - 328

Long term outcomes

Netherlands (1986 – 2016)

- 996 patients with type 1 DM
  - 42% DDKT
  - 16% LDKT
  - 42% SPK

Patient survival



Diabetes Care 2020 ; 43 : 321 - 328

Long term outcomes (2)

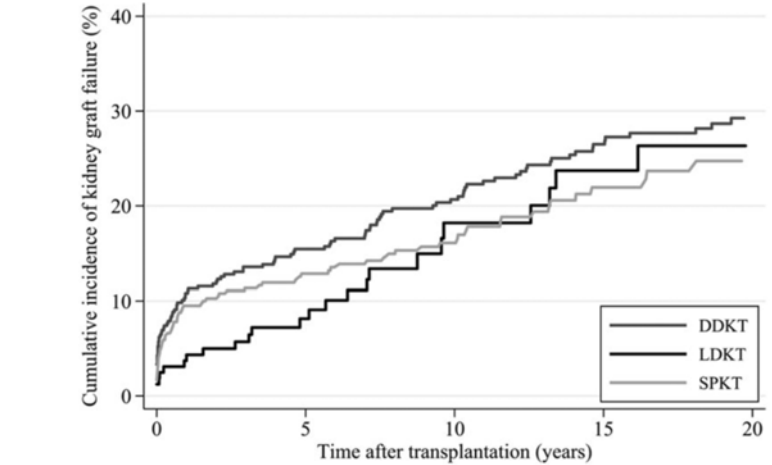
Netherlands (1986 – 2016)

- 996 patients transplanted
  - 42% DDKT
  - 16% LDKT
  - 42% SPK

No difference in graft survival between LDKT and SPK

Pancreas has other protective effects

Cumulative Risk of Renal Failure



Number at risk

DDKT	414	210	103	47	12
LDKT	161	75	26	12	5
SPKT	421	245	152	64	18

Long term outcomes

Patient survival (Six study summary)

Author (year)	Source	Patients (n)	Follow-up	Patient survival
Morath (2010)	CTS (registry data)	n = 15,118	Up to 20 years	SPK > LDK > DDK
Morath (2008)	CTS (registry data)	n = 11,420	Up to 18 years	SPK > LDK > DDK
Sollinger (2009)	Single center (US)	n = 2100	Up to 22 years	SPK > LDK > DDK
Becker (2000)	Single center (US)	n = 642	Up to 33 years	SPK > LDK > DDK
Lindahl (2013)	Single center (EU)	n = 630	Up to 27 years	SPK > LDK > DDK
Mohan (2003)	Single center (EU)	n = 101	Up to 11 years	SPK > DDK

Diabetes Research and Clinical Practice 2014 ; 105 : 14 – 21.

Renal graft failure

Year post transplant	SPK	Deceased donor (only kidney)
1 Year	4%	6%
5 Years	19%	26%
10 Years	34%	53%

↓ Risk of recurrence diabetic nephropathy

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Am J Transpl 2017 ; 17 : 117 – 173.

Effect on long term diabetic complications

- Renal: Dr. Rioretto: at 10 years glomeruli normalize, decreases proteinuria
- Neurological: Small series of cases show improvement at 24 months
- Diabetic Retinopathy: Stabilize damage
- Cardiovascular: Decreases risk cardiovascular death, hypertension, dyslipidemia and atherosclerosis

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Diabet Med 2014 ; 31 : 512 – 521.

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Allogenic islet transplantation

Pancreas (Graft) function

International Pancreas Transplant Registry

Type of transplant	1 – year graft function	3 – year graft function
SPK - Pancreas	89.9%	83.4%
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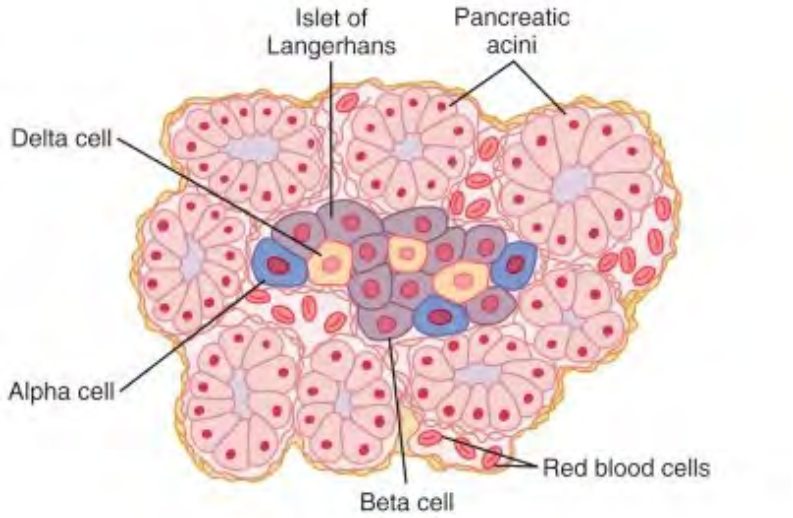
- Causes for graft loss:
  - **0 - 3 months: Technical failure**
    Patient death
  - 4 – 12 months: Patient death
    Immunologic
    Infections
  - > 1 year: Immunologic
    Patient death

Gastroenterol Clin N Am 2018 ; 47 : 417-441.

Normal histology of the pancreas

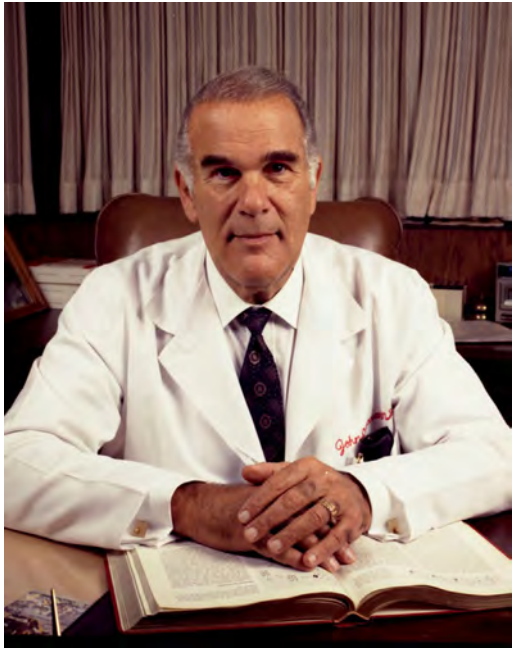
- Acinar cells
- Islets (1 – 2 million cells)
  - 60% beta cells
  - 25% alpha cells
  - 10% delta cells
  - < 5% pp cells
- **Islets approximately 1 – 2% of gland**



Source: Guyton and Hall Textbook of Medical Physiology

History

Universidad of Minnesota



Transplant Proc 1979 ; 11: 336 – 340.
Ann Surg 1980 ; 192 : 526 – 542.

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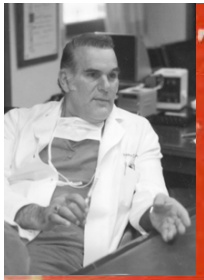
History



TRANSPLANTATION PROCEEDINGS

Human Islet Transplantation: A Preliminary Report

J. S. Najarian, D. E. R. Sutherland, A. J. Matas, M. W. Steffes,
R. L. Simmons, and F. C. Goetz

PANCREATIC islet tissue can be successfully transplanted in animals with induced diabetes.[1–3] Islets are usually isolated from adult pancreas.[3] Neonatal pancreas has a low exocrine enzyme content and can be dispersed and transplanted without separation of islets.[4] We have ob-

antigens was performed,[8] but not as a basis for recipient selection. The donor and recipients shared one antigen in two instances, two antigens in one instance, and no antigens in seven instances. In two instances, the islet and original kidney donor shared an HLA antigen not present in the recipient.

Islet Preparation

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Transplant Proc 1979 ; 11: 336 – 340.

Three major surgical components

1. Pancreas procurement
2. Islet isolation
3. Islet infusion into the portal vein

Islet isolation

Good manufacturing practice (GMP) facility

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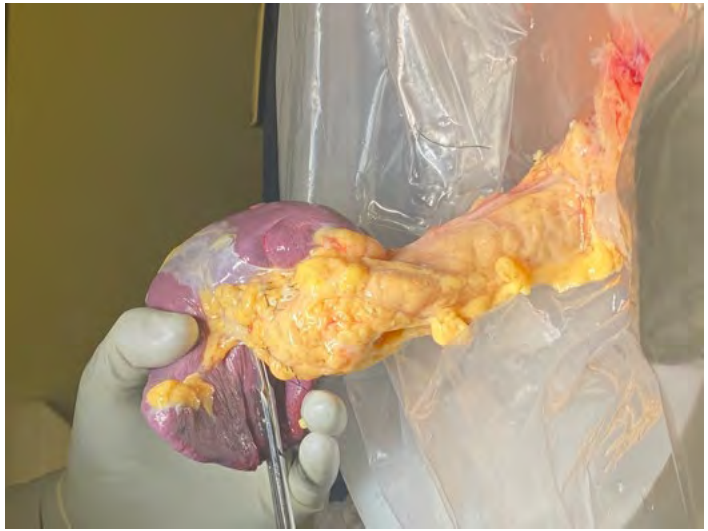
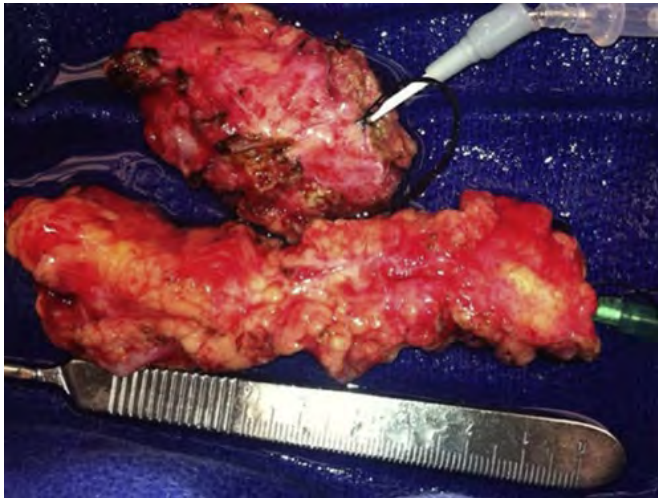
Islet isolation

Preparation of the parenchyma

Spleen and duodenum removed



PD cannulated



Islet isolation

Preparation pancreatic parenchyma

Cold infusion collagenase / proteases

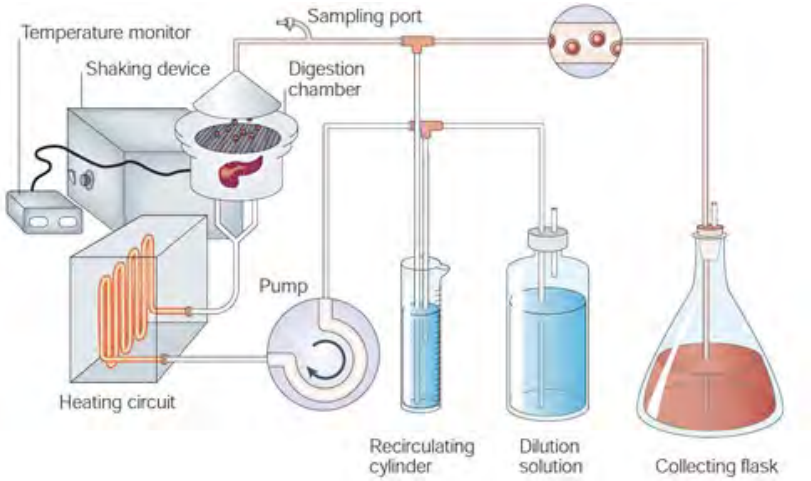
Parenchyma divided

Islet isolation

Preparation of pancreatic parenchyma

Ricordi chamber

Temperature 34 – 37℃

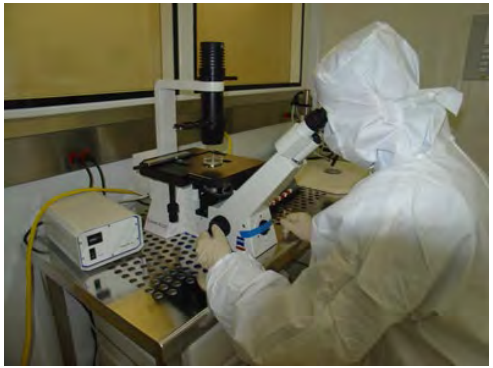


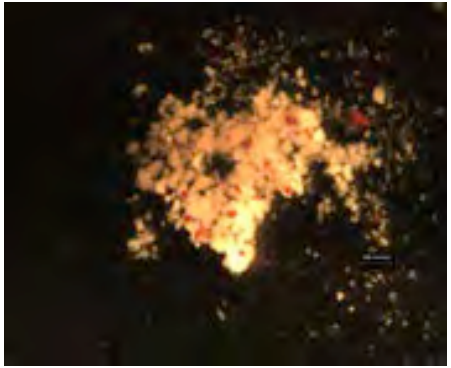
Islet isolation

Islet recollection

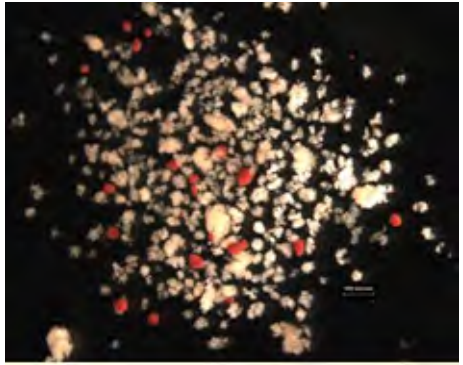
Islet isolation

Dithizone staining





10 min digestion



15 min digestion

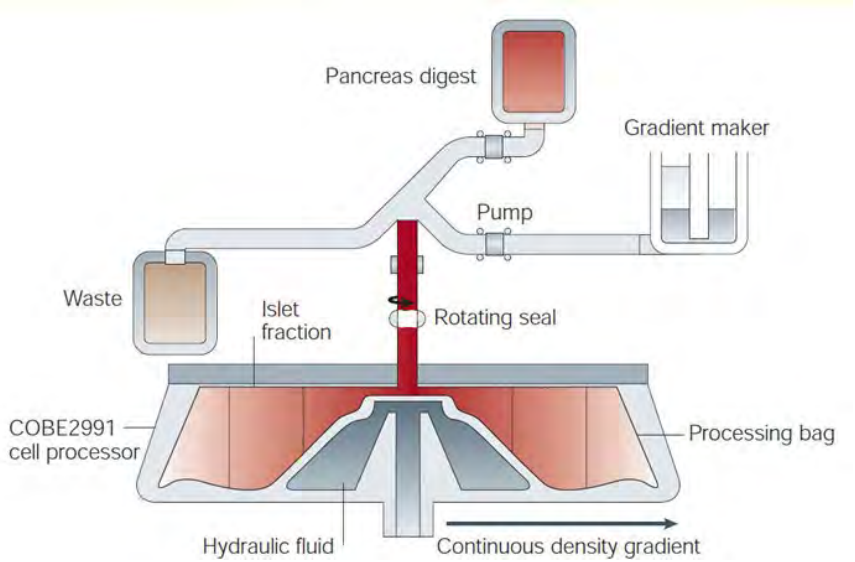
Islet isolation

Islet Purification

Objetive

- < 0.2 to 0.25 ml/kg (max 10 – 15 ml of tissue)
- **Islet loss approximately 10%**

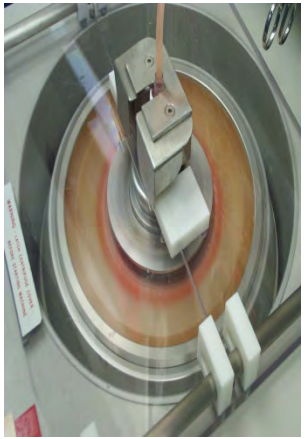
Islet Purification



Endocrine Reviews 2019 ; 40 : 631 – 668.

Islet isolation

Islet Purification



Endocrine Reviews 2019 ; 40 : 631 – 668.

Islet isolation

Final step: Prepare infusion bag

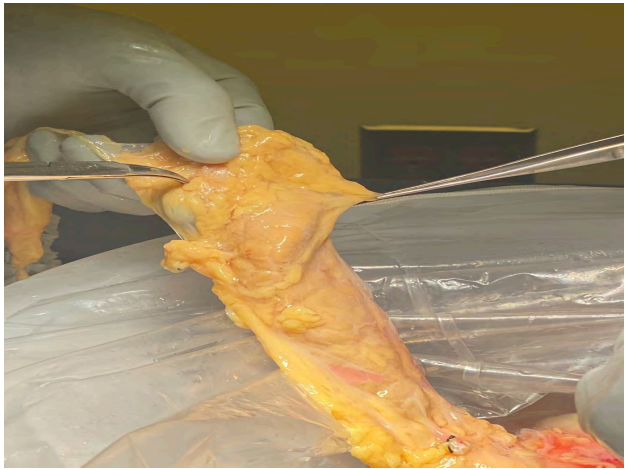
200 cc culture medium CMRL + albumin + ciprofloxacin + heparin

Endocrine Reviews 2019 ; 40 : 631 – 668.

Islet isolation

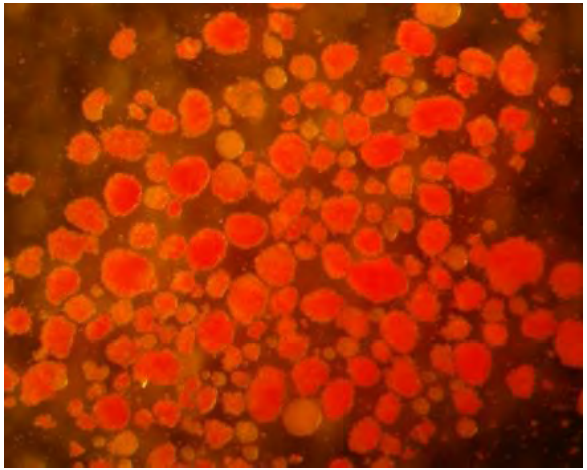
Final result

Before



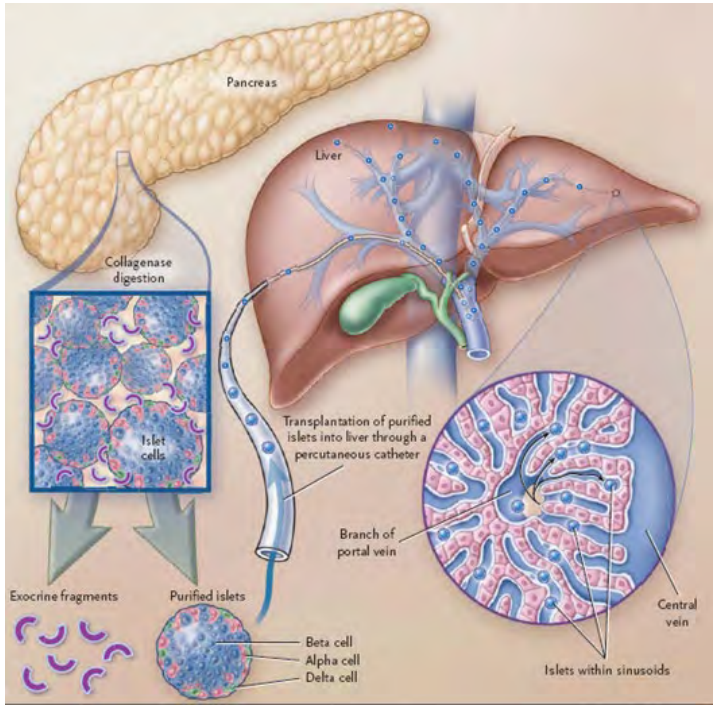
5 to 7 hours

After



- **Islet yield never 100% → Approximately 50 – 60%**

Islet infusion into portal vein



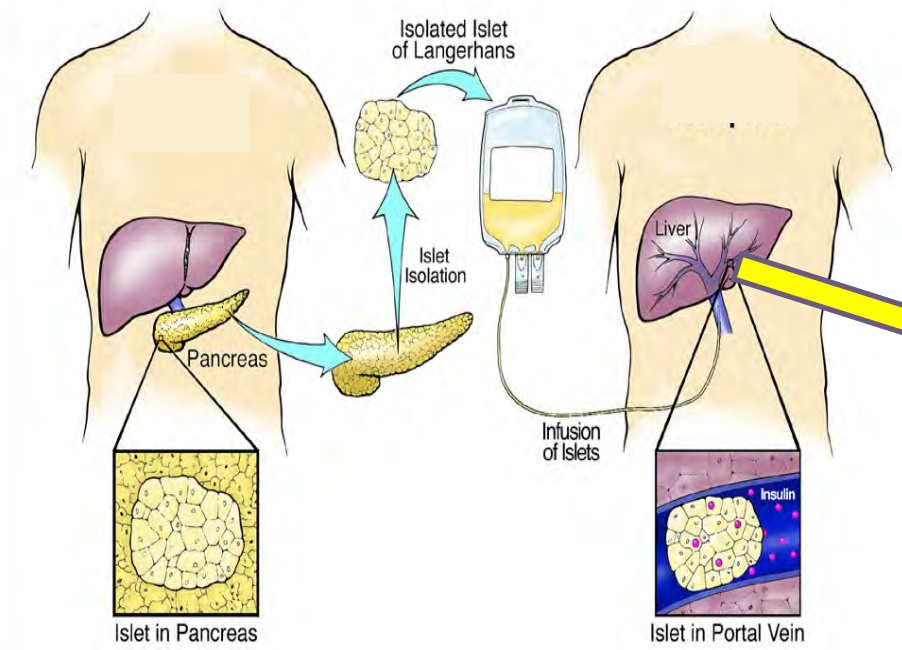
Objetives:

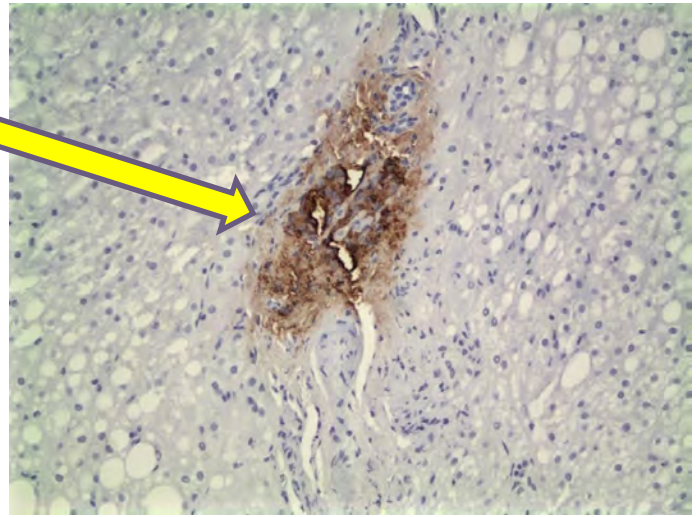
- At least 5,000 IEQ/kg
- Insulin independent 7000 IEQ/kg

N Engl J Med 2004 ; 350 : 694 – 705.

Percutaneous Islet Infusion

Interventional Radiology





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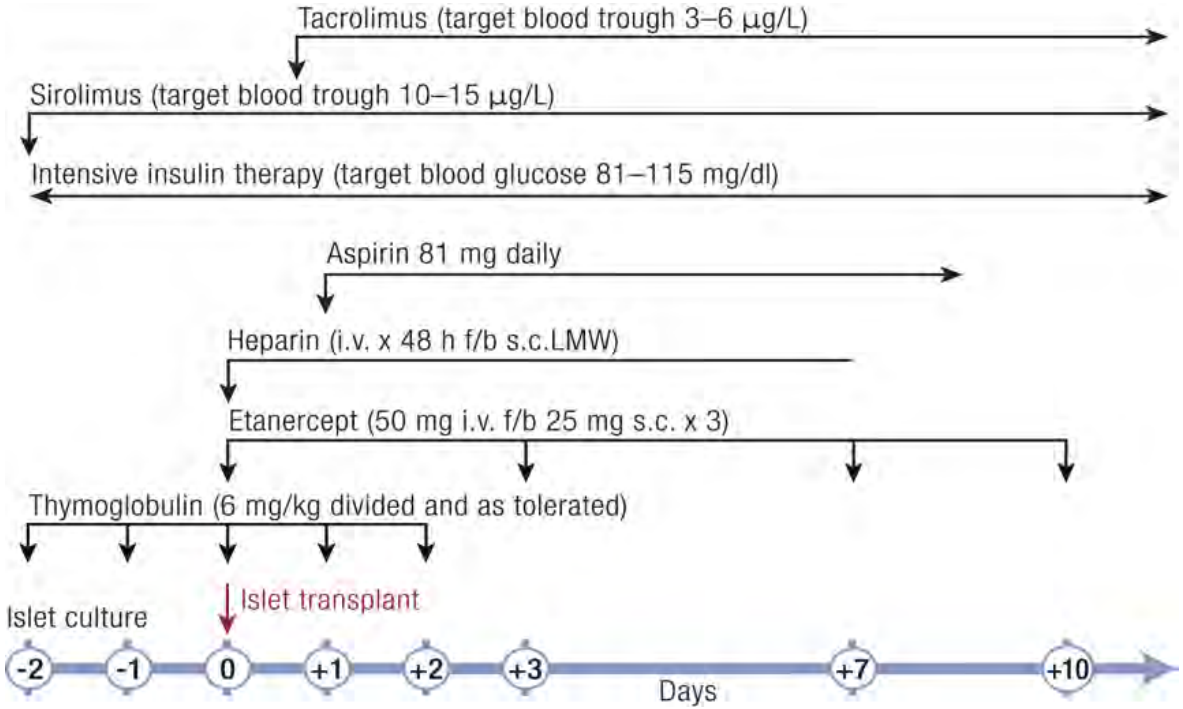
Islet allotransplantation for type 1 Diabetes

Immunosuppression protocol



Endocrine Review 2019 ; 40 : 631 – 668.

Alternative sites for islet infusion

Ideal characteristics

- Adequate blood and Oxygen
- Easy access
- Able to give large quantity
- Minimal inflammatory/immune reaction
- Able to be monitored

Alternative sites

- Renal : subcapsular
- Omentum
- Gastric and intestinal submucosa
- Subcutaneous
- Intrasplenic
- Blood marrow

Curr Opin Organ Transplant 2017 ; 4 : 364 – 371.

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Outcomes after islet transplantation

Islet allotransplantation for type 1 Diabetes

Clinical Islet Transplantation (CIT) Consortium Results (CIT– 07)

Inclusion criteria

- 18 – 65 years
- DM Type 1 ≥ 5 years
- Absent C – Peptide
- Impaired awareness hypoglycemia / marked glycemic lability
- Severe hypoglycemia (prior 12 months) *
- *** Certified by endocrinologist/diabetologist**

Endpoints

- Primary (ADA)
  - HbA1c <7% day 365
  - Freedom SHE day 28 – 365
- Secondary (AACE)
  - HbA1c < 6.5% day 365
  - Freedom SHE day 28 – 365
  - Insulin independence 7-day period

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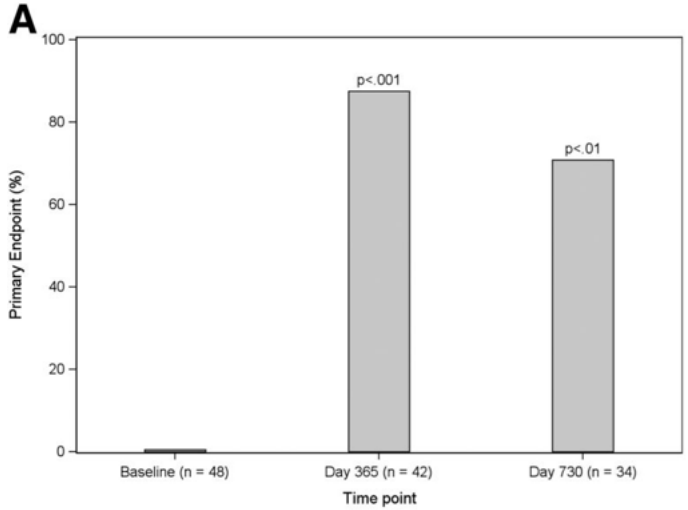
Islet allotransplantation for type 1 Diabetes

Clinical Islet Transplantation (CIT) Consortium Results (CIT– 07)

Results

- 48 subjects received 75 PHPI
  - 42 (87.5%) achieved primary endpoint
  - One infusion – 22 (45.8%)
  - Two infusions – 25 (52.1%)
  - Three infusions - 1 (2.0%)

Primary endpoint after 365 days



Diabetes Care 2016 ; 39 : 1230 - 1240

Islet allotransplantation for type 1 Diabetes

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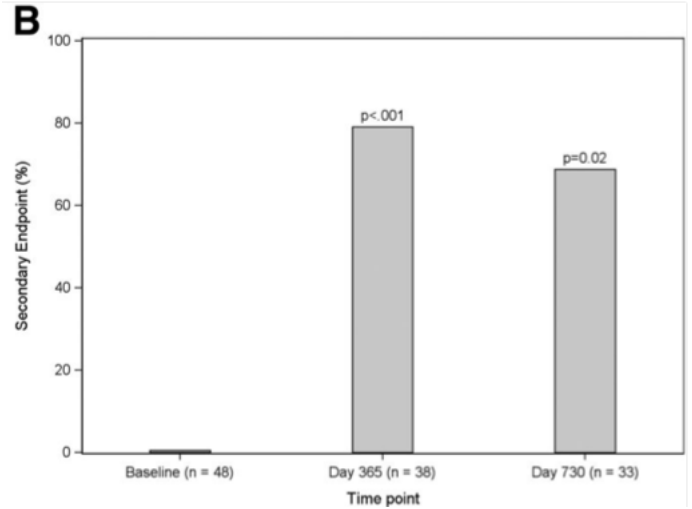

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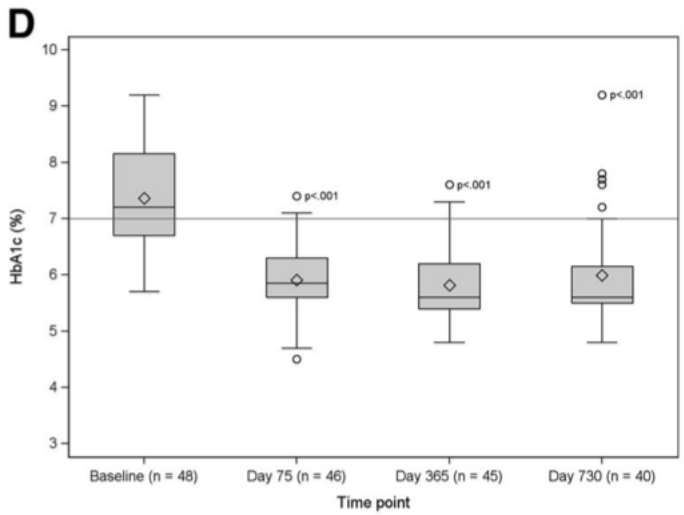
Hemoglobin A1c Levels



Diabetes Care 2016 ; 39 : 1230 - 1240

Islet allotransplantation for type 1 Diabetes

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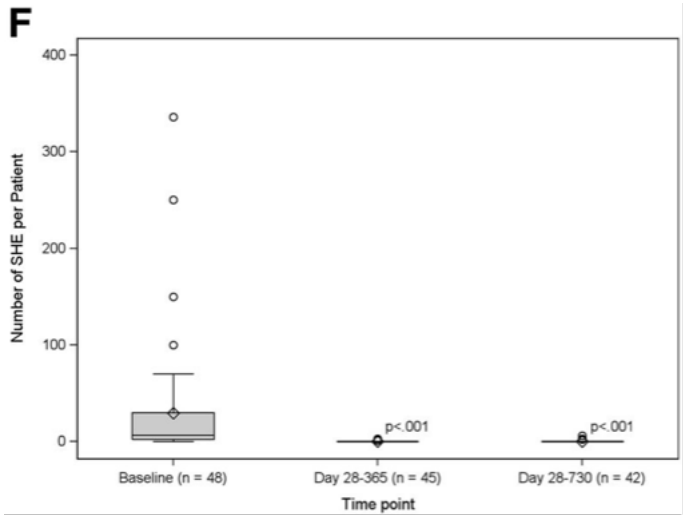
Subjects with severe hypoglycemia

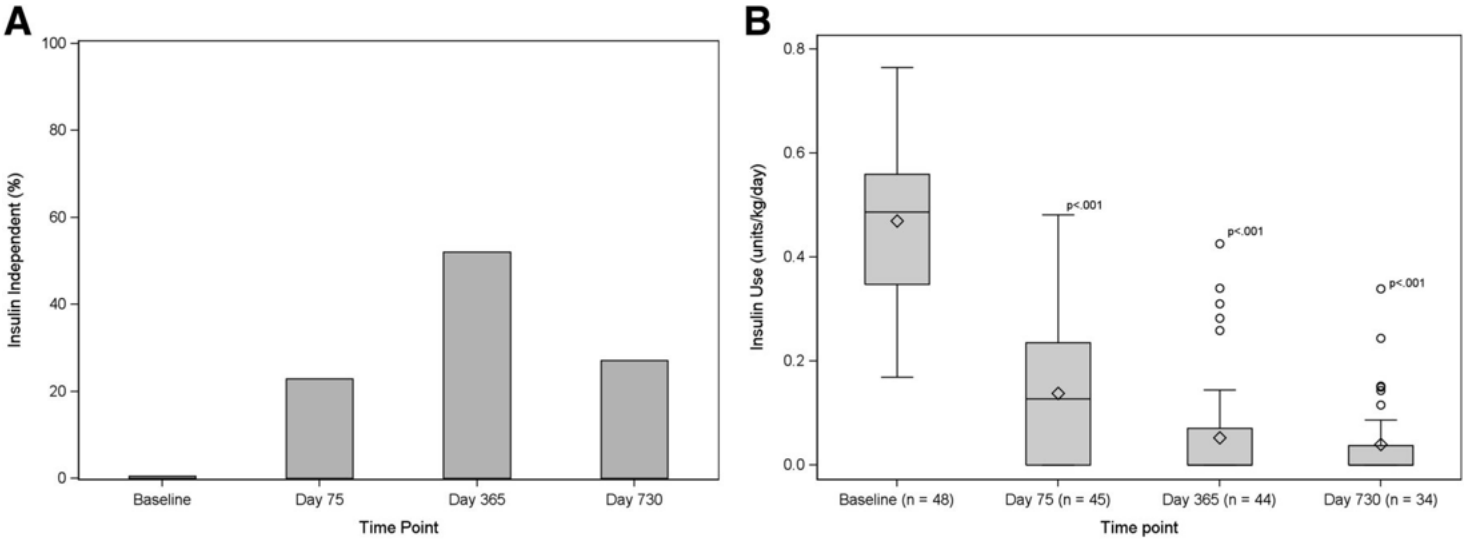


Diabetes Care 2016 ; 39 : 1230 - 1240

Islet allotransplantation for type 1 Diabetes

Clinical Islet Transplantation (CIT) Consortium Results (CIT– 07)

Insulin requirements

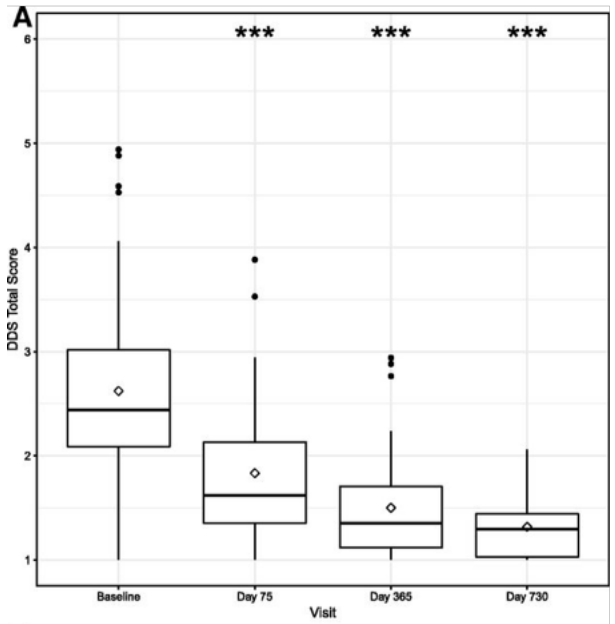


Diabetes Care 2016 ; 39 : 1230 - 1240

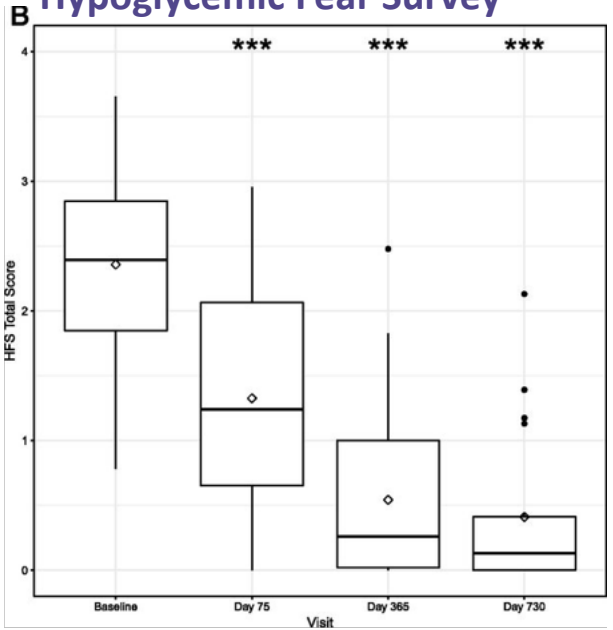
Islet allotransplantation for type 1 Diabetes

Effect on Quality of Life (CIT – 07)

Diabetes Distress Score



Hypoglycemic Fear Survey



Diabetes Care 2018 ; 41: 1001 -1008.

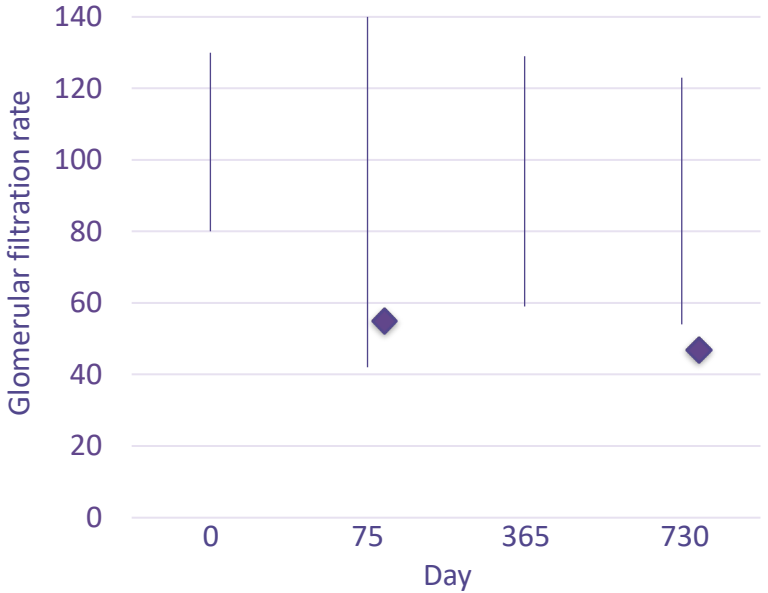
Islet allotransplantation for type 1 Diabetes

Complications CIT - 07

Adverse events:

- Postprocedural bleeding 8.9%
- Sensitization 6 patients (PRA 2%, 14%, 29%, 64%, 74%, and 98%)
- Decrease in GFR

Glomerular Filtration Rate CIT – 07

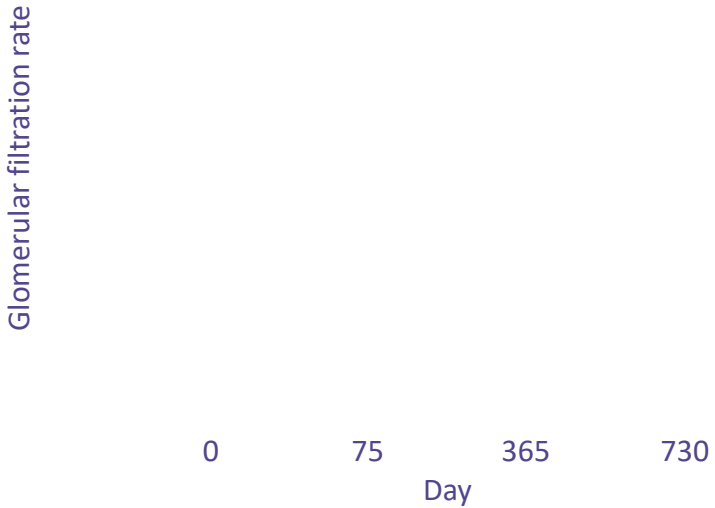


Diabetes Care 2018 ; 41: 1001 -1008.

Islet allotransplantation for type 1 Diabetes

Are SPKs comparable to SIK ?

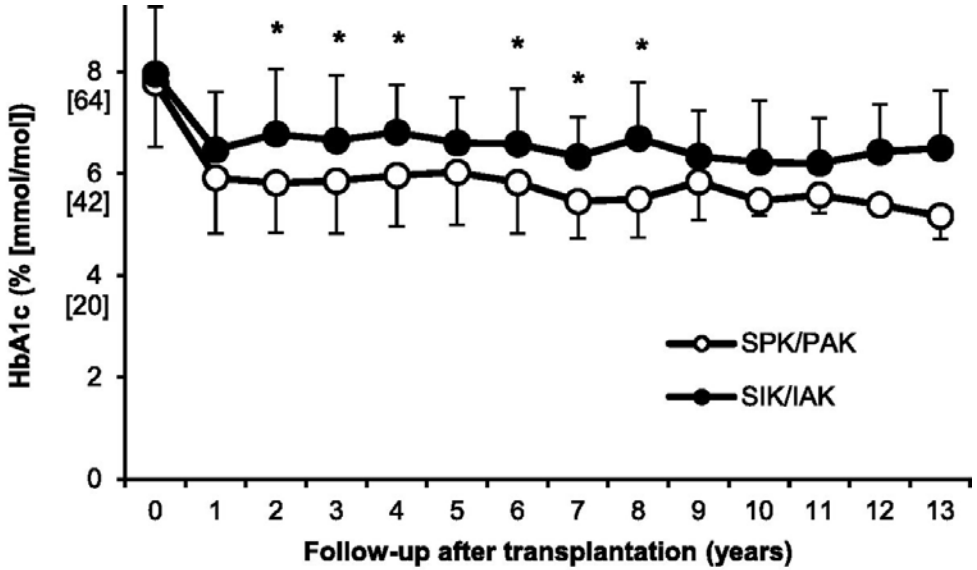
- University Hospital Zurich
- Jan 2000 – December 2013
- Immunosupression (SPK or PAK)
  - TAC + MMF + PDN
  - Basiliximab (2012) Thymoglobulin
- Immunosuppression (SIK or IAK)
  - TAC (7 – 10) + Sirolimus (3 – 6)
  - Daclizumab (2012) Thymoglobulin



Diabetes Care 2015 ; 38: 752 - 759.

Islet allotransplantation for type 1 Diabetes

Are SPKs comparable to SIK ?

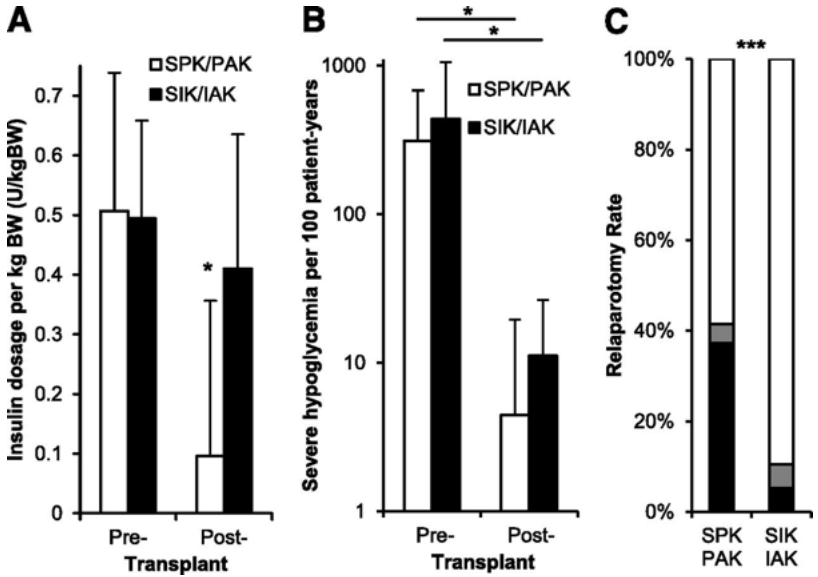


n (SPK/PAK)	86	71	61	45	38	31	23	15	14	13	11	6	6
n (SIK/IAK)	37	30	27	25	18	15	14	9	8	6	4	4	3

Diabetes Care 2015 ; 38: 752 - 759.

Islet allotransplantation for type 1 Diabetes

Are SPKs comparable to SIK ?



Baseline characteristics

	SPK / PAK	SIK / IAK
Age at transplant	44.2 ± 7.6	51.8 ± 9.0
Duration DM	32.1 ± 8.2	37 ± 1
Donor age	32.6 ± 12.1	53.4 ± 8.1
Donor BMI	23.2 ± 3.2	25.9 ± 2.7
CIT	561 ± 180.6	325.6 ± 81.6

Diabetes Care 2015 ; 38: 752 - 759.

Conclusions

- Not every patient with Diabetes Mellitus is a candidate
- Suboptimal use of pancreas transplant in the United States
- Best modality of therapy in patients with DM and ESRD
- Improves quality of life and most likely chronic complications
- **“Added survival benefit if pancreas doesn’t fail”**
- “Complicated surgical procedure”

Questions?

Daniel.Borja-Cacho@nm.org

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