Islet transplantation for the treatment of diabetes: Progress and Challenges

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Type 1 diabetes

Autoimmune destruction of beta cells

Hyperglycemia

Insulin
Type 1 diabetes

The number of adults with diabetes has doubled world-wide over the last three decades to nearly 350 million

5-15% of cases of diabetes worldwide

0.24% of W. European pop

Incidence/100,000 pop:
- 9.2 new cases in Switzerland
- 57.6 new cases in Finland
- 4.6 new cases in Georgia

Selective autoimmune destruction of b-cells

✝ b-cell replacement
Insulin

Banting & Best
1921 - isolation of insulin  
1922 - first patient treated  
1923 : Nobel Prize
Insulin is NOT a cure. It's LIFE SUPPORT!

INSULIN IS NOT A CURE FOR DIABETES. IT JUST KEEPS PEOPLE ALIVE UNTIL WE FIND ONE.

Support the Research of the American Diabetes Association

Progression of diabetic disease

- Retinopathy ➔ blindness
- Nephropathy ➔ dialysis
- Macroangiopathy ➔ amputation, myocardial infarction
Physiologic b-cell replacement

Perfectly timed insulin release

Keep glucose in normal range

Function for entire lifetime
Main Contributors

John Najarian
David Sutherland (1977)

Camillo Ricordi
Automated method (1989)

Bernhard Hering
Giessen/Minnesota
Geneva, Milan

James Shapiro (2000)

Paul Lacy
Colin Weber
Ray Rajotte
David Scharp
... many others
Automated method for human islet isolation

“Insulin independence after solitary islet transplantation in type 1 diabetic patients using steroid-free immunosuppression”

Shapiro AMJ et al, NEJM 2000; 343:230

- 7 consecutive patients achieved euglycemia during a mean follow-up of 11 months, with normal HgbA1c and GTT

- 6/7 patients required >1 donor (>1 transplant) a median of 29 days from the first procedure

- Mean islet equivalents =11,400/kg required to achieve euglycemia

- Cadaveric pancreata from older donors >45 yo (70% would have been discarded)
Islet Transplant Activity (1999-2011)

Estimated 400 patients at 35 institutions - 80% success
Indications for Tx

- Type 1 DM + end-stage kidney failure: Simultaneous islet-kidney Tx (SIK)

- Type 1 DM in kidney graft recipient: Islet after kidney Tx (IAK)

- Treatment of chronic complications of diabetes
Indications for Tx

- Brittle type 1 diabetes, severe hypoglycemia

- Islet Tx alone (ITA)

- Treatment of acute complications of diabetes/insulin therapy
Indications for Tx

- Isolation fails 50% of time
- Side effects of anti-rejection, anti-autoimmunity immunosuppressive drugs

Statistics:
- 6,182 available organs (US)
- Only 23.8% procured/used
- ~ 400 organs for islets

Challenges for Islet Transplantation

- Procurement and cold ischemic damage to donor pancreas
- 2-3 donor organ islets/recipient
- Labour intensive and relatively inconsistent islet isolation
- Isolation fails 50% of time

- Side effects of anti-rejection, anti-autoimmunity immunosuppressive drugs
- Ectopic intravascular site
- Activation of damaging non-immune inflammatory pathways

Long-term “success”:
- 80% at 1 yr → ~ 20% at 5 yrs
- Recipient autoimmunity and alloimmunity
Future of Cell Therapy for Diabetes

- Perform islet transplantation without chronic immunosuppression
- Create a “universal donor” source of insulin-secreting cells for transplantation
- Stem Cells, Tissue reprogramming, regeneration of beta cells
- Immune Tolerance
- Tissue Engineering
- Hybrid Devices and Local Delivery of IS/IM
- Find alternative implantation site
Isolated small intestinal segments support auxiliary livers with maintenance of hepatic functions

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Hypothesis

Small intestinal submucosa would serve as a suitable place for pancreatic islet transplantation.
Priorities of IS Site

- Extravascular site
- Portal drainage
- Well vascularized environment
- Naturally enriched in collagen types I, III and VI, glycosaminoglycans (hyaluronic acid, chondroitin sulfate A and B, heparin, heparan sulfate), proteoglycans, fibronectin
- Several growth factors required for angiogenesis and cell growth are expressed in the intestinal submucosa (VEGF, FGF, HGF, and TGF-b)
Materials and Methods

Fabrication of intestinal segments and islet transplantation

Lewis Rats

STZ diabetic Lewis Rats
Pancreatic Islet Tx into the intestinal submucosa induces euglicemia

Stz diabetic Lewis Rats (n=20)

IS Tx & IP Tx
500 IEQ

IS graft removal: 1 w, 2 w, 1.5 m, 3 m, 6 m

Blood Glucose (mg/Dl)

Days after Tx

0 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112 119 126 133 140 147 154 161 168 175 182 189

Blood Glucose (mg/Dl)

0 100 200 300 400 500 600 700

0 min 15 min 30 min 60 min 120 min

POD 7

Intestine

Islets
Long-term engraftment and function of transplanted pancreatic islets in vascularized segments of small intestine

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Keywords
islets, pancreas, portal vein, small intestine, transplantation.

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Summary
This study evaluated the potential of vascularized small intestinal segments for pancreatic islet transplantation. Islets isolated from Lewis rats were transplanted into diabetic syngeneic recipients. Segments of small intestine were prepared by denudation of the mucosal layer prior to implantation of pancreatic islets into the segments. Animal groups were established to determine engraftment, survival and function of islets transplanted into either intestinal segments or portal vein over up to 60 days. We found transplantation of functionally intact pancreatic islets into small intestinal segments was well tolerated. Transplanted islets were rapidly engrafted in intestinal segments as demonstrated vascularization and expression of insulin and glucagon throughout the 60-day duration of the studies. Transplantation of islets restored euglycemia in diabetic rats, which was similar to animals receiving islets intraportally. Moreover, animals treated with islet transplants showed normal responses to glucose challenges. Removal of graft-bearing intestinal segments led to recurrence of hyperglycemia indicating that transplanted islets were responsible for improved outcomes. Therefore, we concluded that vascularized intestinal segments supported reorganization, survival and function of transplanted islets with therapeutic efficacy in streptozotocin-treated diabetic rats. The approach described here will be appropriate for studying islet biogenesis, reorganization and function, including for cell therapy applications.
Intestinal Submucosal Site vs Liver

Stz diabetic Lewis Rats (n=20)

IS Tx vs IP Tx
350 IEQ

IS graft removal: 1 w, 2 w, 1.5 m, 3 m, 6 m, 9m, 12 m

Weeks after Tx

Blood Glucose (mg/dl)

0 2 3 4 5 6 8 10 12 16 20 24 32 40 44 48

IS Site
Liver

Month after Tx

0 1 2 3 4 5 6 7

Survival (%)

IS Site
Liver
Vascular casting of graft bearing intestinal segment
Conclusions

• Our studies demonstrate that pancreatic islets can be successfully transplanted into vascularized small intestinal segments with the potential to correct hyperglycemia in diabetic rats

• Islets transplanted in intestinal segments had normal morphology, and maintained expression of insulin as well as glucagon.

• These encouraging features of the isolated intestinal segment open new research avenues for addressing biological mechanisms and clinical applications.

• This tissue-engineering approach could eventually be considered for cell therapy in diabetes mellitus.
An Isolated Venous Sac as a Novel Site for Cell Therapy in Diabetes Mellitus

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Background. Transplanting pancreatic islets is of significant interest for type 1 diabetes mellitus. After intraportal injection of islets, inferior engraftment and eventual loss of transplanted islets constitute major limitations. Therefore, alternative approaches will be helpful. Here, we evaluated in animals whether an isolated venous sac would support survival of transplanted islets, along with correction of hyperglycemia.

Methods. Pancreatic islets isolated from adult Lewis rats were transplanted either into an isolated venous sac made from lumbar vein or into the portal vein of syngeneic rats. The integrity and vascular organization of the venous sac was determined by studies of the local microcirculation. The engraftment, survival, and function of transplanted islets were analyzed by histology, including endocrine function in situ and by glycemic control in rats with streptozotocin-induced diabetes.

Results. Transplanted islets showed normal morphology with insulin expression in isolated venous sac during the long term. Transplanted islets received blood supply from vasa vasorum and had access to drainage through venous tributaries in the venous sac. This resulted in restoration of euglycemia in diabetic rats. Removal of islet graft-bearing venous sac in diabetic rats led to recurrence of hyperglycemia. By contrast, euglycemia was not restored in rats treated by intraportal transplantation of islets.

Conclusions. We demonstrated that pancreatic islets successfully engrafted and functioned in the isolated venous sac with ability to restore euglycemia in diabetic rats. Therefore, the isolated venous sac offers a new site for transplantation of pancreatic islets. This would be clinically beneficial as an alternative to intrahepatic islet transplantation.

Keywords: Islets, Pancreas, Intravascular transplantation.

(Transplantation 2012;94: 319–324)
Materials and Methods

Fabrication of venous sac and islet transplantation

Lewis Rats

STZ diabetic Lewis Rats

A

B

C

D
Pancreatic Islet Tx into the venous sac induces euglicemia.

IV Tx & IP Tx
350 IEQ
Stz diabetic Lewis Rats (n=20)

IV graft removal: 3 d, 7 d, 14 d, 60d
Histopathological evaluation of explanted islet-containing venous sacs
Integrity and vascular supply of venous sacs

(A) Vascular casts obtained with latex dye of lumbar vessels showing vasa vasorum in healthy rat.

(B) Vascular casts in rat 3 d after islet transplantation showing patent vessels and vasa vasorum
Regulation of blood glucose levels in diabetic rats after islet transplantation
Conclusions

• Our studies demonstrate that venous sac permitted engraftment, survival and function of transplanted pancreatic islets over the long-term.

• Even a minimal mass of pancreatic islets in isolated venous sacs was successful in restoring euglycemia in STZ-treated diabetic rats.

• the venous sac should be useful for testing the fate and function of stem cell-derived pancreatic beta cells or islets in the future.

• The simplicity of transplanting islets in venous sac should advance studies for clinical development.
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Thank You!

Mesenchymal stem cells forming a beautiful heart shape. Image copyright Sarah Ranjbarvaziri, of Dalhousie University, Canada.