

Islet Cell Transplants

Current status and patient selection

Islet Cell Transplants

- Research Procedure Only
 - American Diabetes Association 2006 Guidelines
- Current Data
 - Transient insulin independence (44% 1yr, 10% 5yrs)
 - Majority have controlled severe hypoglycaemia with partial graft function
- Many potential avenues for improved outcomes justifies further research
 - Patient selection focussed severe, uncontrollable hypoglycaemia group

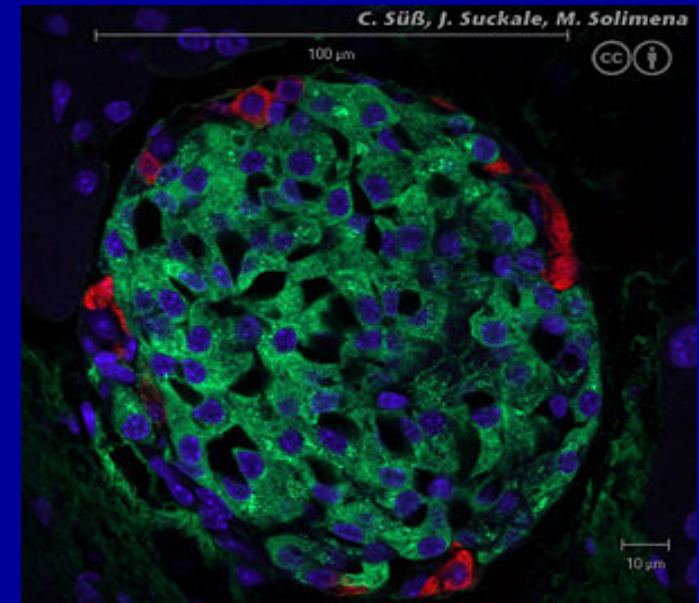
SA/NT Islet cell transplant project

Potential recipient

- 57 yr woman, school teacher
- T1DM 33 years
- Retinopathy/laser, minimal peripheral neuropathy, no autonomic neuropathy, normal urine albumin, and CrCl
- Severe hypoglycaemia events: 1-4 per month, marked hypoglycaemia awareness, chaotic BGLs, HbA1c 7.4%
- Management CSII: optimized over 4 years, surveillance home (husband), work by colleagues – won court trial against employer to allow giving of glucagon by work mate
- Reduces personal freedom and that of others, compromises travel, led to conflict in workplace

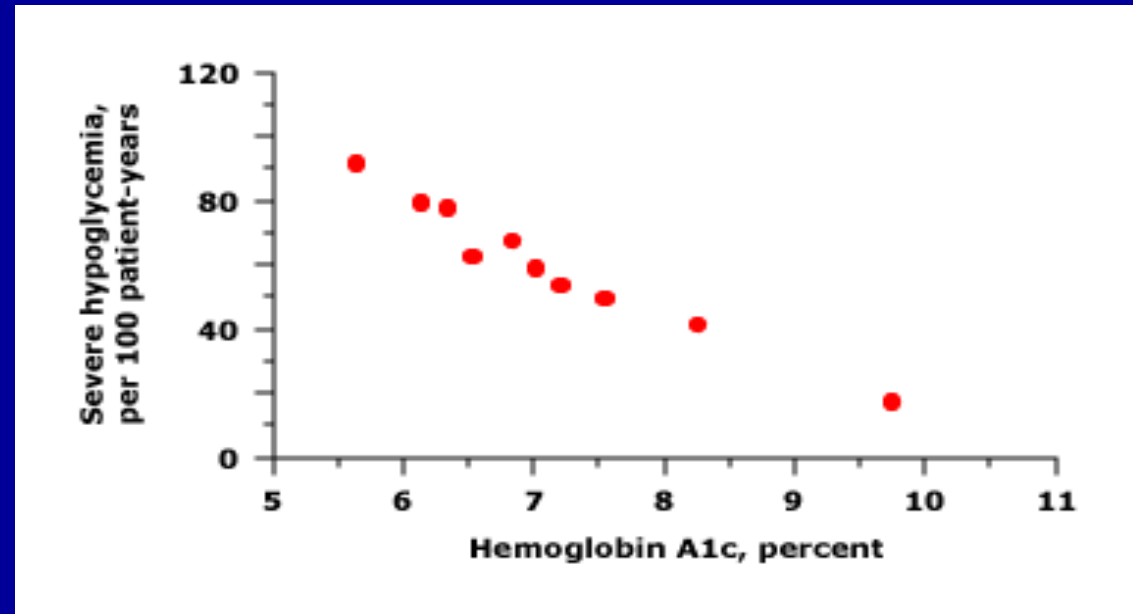
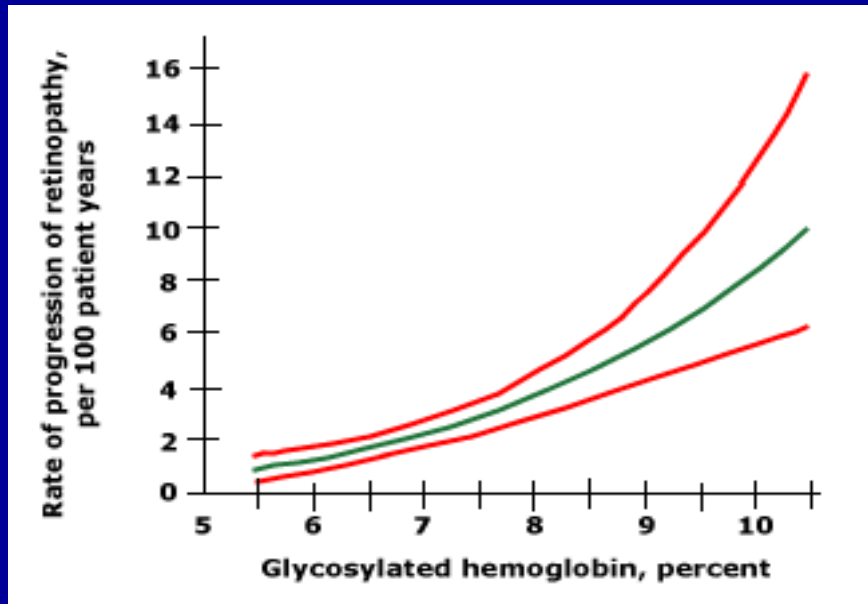
Type 1 diabetes: Islet cells

- T1DM: 5-10% all diabetes
- Incidence ↑ Australian children 3%/yr
- Genetically predisposed individuals
- Autoimmune destruction beta cells, leading to hyperglycaemia developing over several years
- Postprandial – Fasting – weight loss – ketosis
 - Early treatment [preserved beta cell function] straightforward
 - Later increased risk of mild hypoglycaemia
 - Eventual increased risk severe hypoglycaemia [subgroup]



1-2% pancreas volume
1 million islet cells

Diabetes Control and Complications Trial



Retinopathy – HbA1c

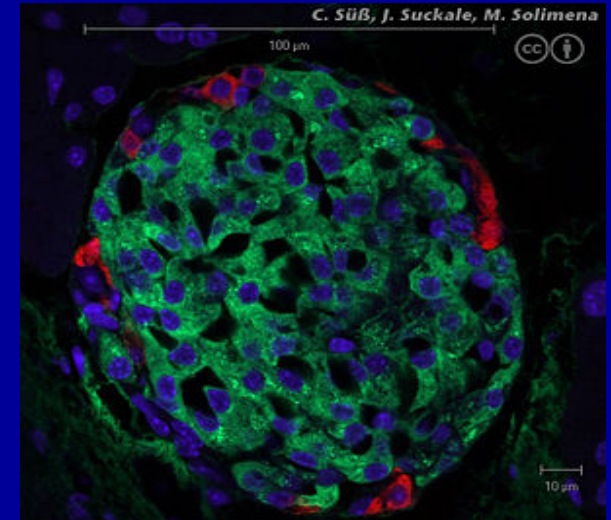
Hypoglycaemia – HbA1c

Hypoglycaemia limits ability to control HbA1c – 7% optimal epidemiologically

Physiological response to hypoglycaemia

- Insulin secretion off (<4.4 mmol/L)
- Glucagon rises (3.9)
- Adrenaline rises (3.9)
- GH and cortisol rise (3.3)

- Hyperadrenergic symptoms (3.3)
- Neuroglycopaenia (2.8)
 - Lack hyperadrenergic symptoms =
“loss hypoglycaemia awareness”



Hypoglycaemia – severe and mild

- Overall prevalence of severe hypoglycaemia 30%/yr [biological risk factors]
- Mild hypoglycaemia 1-2 per week [life style factors]
- 70% of severe hypoglycaemia in 5% of patients
- 30% severe episodes lead to coma

Risk factors

- Loss of hypoglycaemia awareness (25% T1DM – variable severity)
- Long duration diabetes; age
- Strict control (7% vs 9%; 3-fold increased risk)
- C-peptide negative
- ACE system (AG), ACE I/D, AT2R1 genotypes (?)
 - Sleep – blunts adrenergic response

Hypoglycaemia reduction strategies

- Lifestyle changes – minimize impact events, match food/insulin, exercise (food/insulin and exercise peak), glucagon with relatives, adjusting glycaemic target, drugs (rarely) β -blockers generally unnecessarily implicated J Intern Med. 2001 250:11-7
- Insulin analogues
 - Short acting - avoid late post-prandial hypos
 - Basal analogues – Glargine, detemir – reduce nocturnal hypos
 - ***Data relate to mild hypos studies, effect on severe hypos unproven, one survey showed no change in severe hypos since introduction***
Diabetes Metab Res Rev 2004;20:479
- Continuous subcutaneous insulin infusion (“the pump”): 50%↓
 - FP glucose monitoring, multiple basal rates, boluses
- Islet cell transplants
 - patients willing to be experimental subjects, if available protocol

Pump therapy: hypoglycaemia and HbA1c

- Recent meta-analyses and studies
 - Hypoglycaemia frequency reduced by 50%
 - HbA1c reduced 0.4%
- Data unblinded, extensive education includes better food/insulin matching, close monitoring and self-selection
- Doubles cost of T1 diabetes management from around \$3,500 to \$7,000 p.a.
- Used approx 1% T1DM patients Australia, 25% USA, intermediate through Europe
 - Funding, patient and doctor enthusiasm
 - UK funded for combination HbA1c elevation and hypoglycaemia frequency

Islet cell transplants

- Islet cell transplantation
 - Harvesting 500,000 islet cells cadaver donors, usually 2-3 donors* required
 - Infusion into portal vein for hepatic uptake*
 - Immunosuppression: T cell monoclonal antibody, calcineurin inhibitor (renal/beta cell toxic) and antimetabolite (e.g., mycophenylate)*

Pancreas transplants

- From 1966, most from 1990s
- Pancreas grafted to iliac vessels, drain exocrine to bladder (or bowel) – source cadaver, few hemi-pancreas from live donor
- International Registry shows 2000 per year, 94% with kidney, 6% alone
- One-year graft survival 95% with kidney, 76% pancreas alone [rejection detection]
- Rejection lags behind kidney generally
- Monitor with urine amylase, BGLs
- Excellent results on diabetic complications
- ADA recommendation pancreas alone: Consistent failure insulin-based therapy to control glycaemia and prevent diabetic complications, clinical and emotional problems with insulin Rx

Islet cell transplantation

- Promise: less invasive, procedurally safer than pancreas transplant
- Early studies islet autografts from resected pancreas in chronic pancreatitis patients 70% successful at 2 years
 - No need for immunosuppression
 - Do not have beta cell autoimmune process

Islet cell transplantation

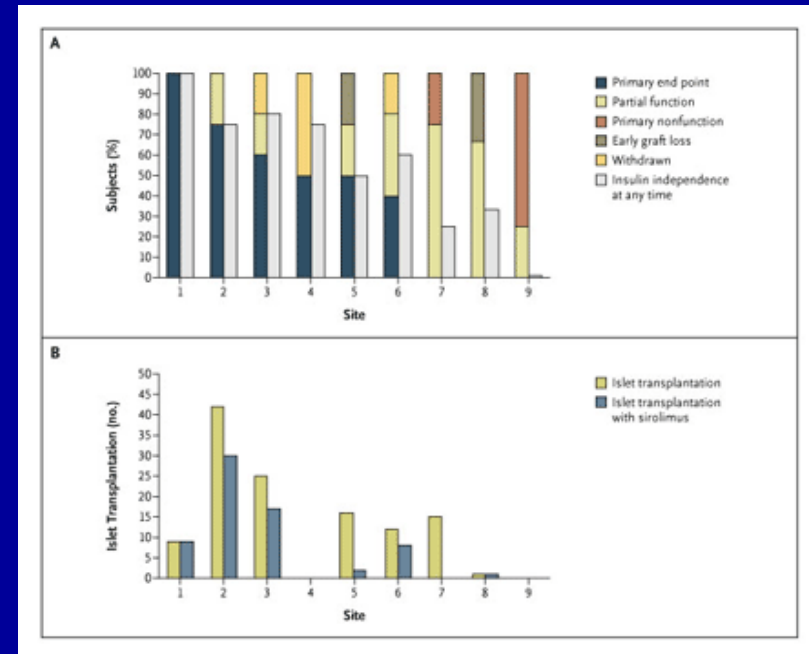
- 2000, Univ Alberta, Edmonton – reported 7 patients, 11,500 islets IEQs/kg cadaver source, isolated collagenase, purified, immediately infused, no glucocorticoids used
 - all normal HbA1c off insulin at 1 year Shapiro et al. N Engl J Med 2000;343:230.
- Led to International Trial of Edmonton Protocol
 - Infusion 500,000 IEQ (10,000/kg)
 - Dacluzimab, sirolimus, tacrolimus

Edmonton International Trial

- 36 patients/nine sites
- 500,000 IEQ infused, up to 3 infusions
 - 1- 31%, 2-25%, 3- 44%
- F/U 37-50 months
- Recipients
 - T1DM, severe hypoglycaemia [97%] or severe glucose lability
 - Wt <70kg F, <75kg M
 - Insulin dose < 0.7U/kg/d
 - CrCl > 80ml/min/1.73m²
- Donors
 - 15-70 years, islets infused within 2 hrs

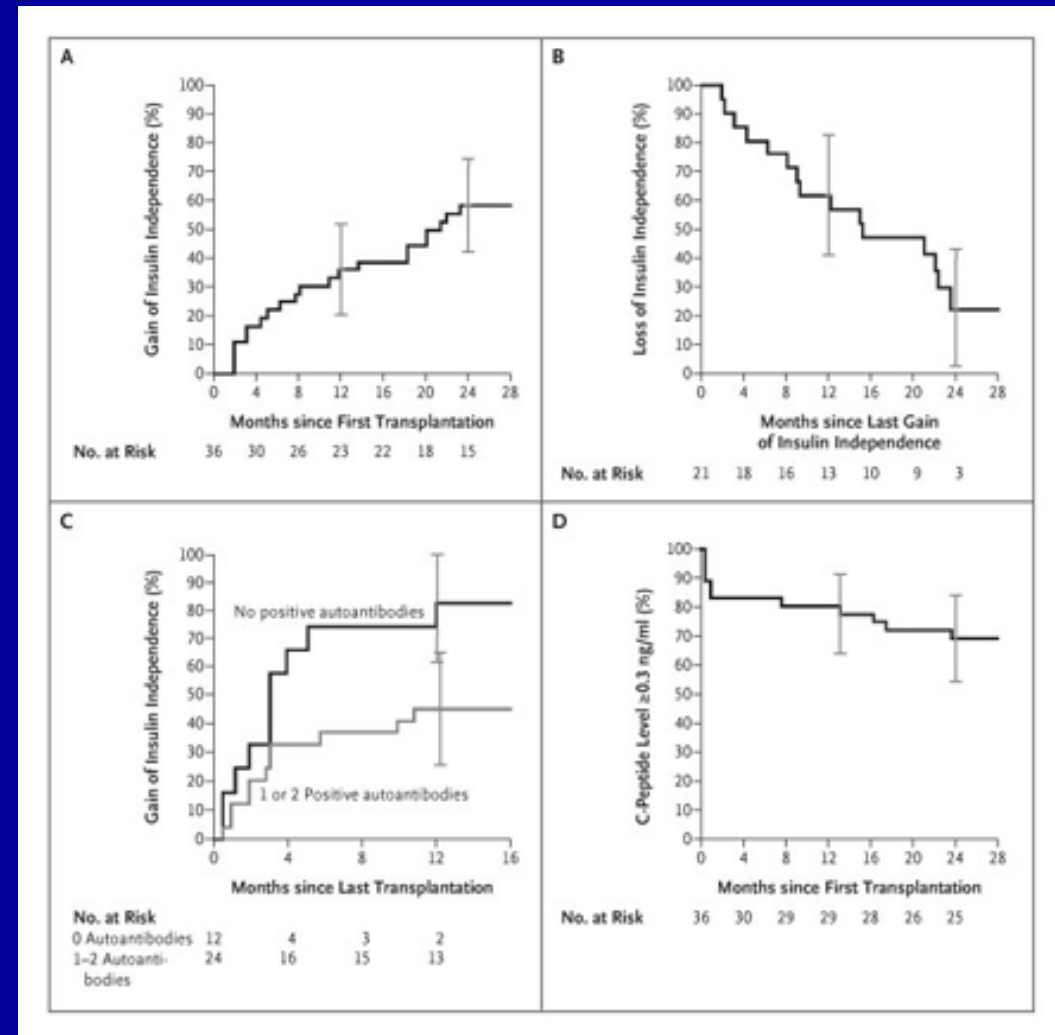
Edmonton Trial: Insulin independence

- **Insulin independence (One year)**
 - 44% insulin independent (near normoglycaemia)
 - 28% partial graft function (C-peptide pos., need insulin)
 - 28% graft failure (C-peptide negative)
- **Two years: 22% insulin independent**
- **Five years: 10% insulin independent (Edmonton subjects)**
- **High variability between sites: 0-100% had patients achieve insulin independence at any time**



Hypoglycaemia and graft function

- Gain/loss islet cell function
- Relationship between no islet autoantibodies prior last infusion and attainment insulin independence $P=0.03$
- Partial graft function (70% 2 yrs) eliminated severe hypoglycaemia



Edmonton Trial: adverse events

- No deaths
- Immunosuppression
 - mouth ulcers, leukopaenia, GI upset, fatigue
- Renal dysfunction
 - Loss of 5ml/min/1.73 m² per year
- Sensitization
 - Multiple HLA mismatches from several donors
 - 31% new HLA antibodies, increase on stopping immunosuppressants

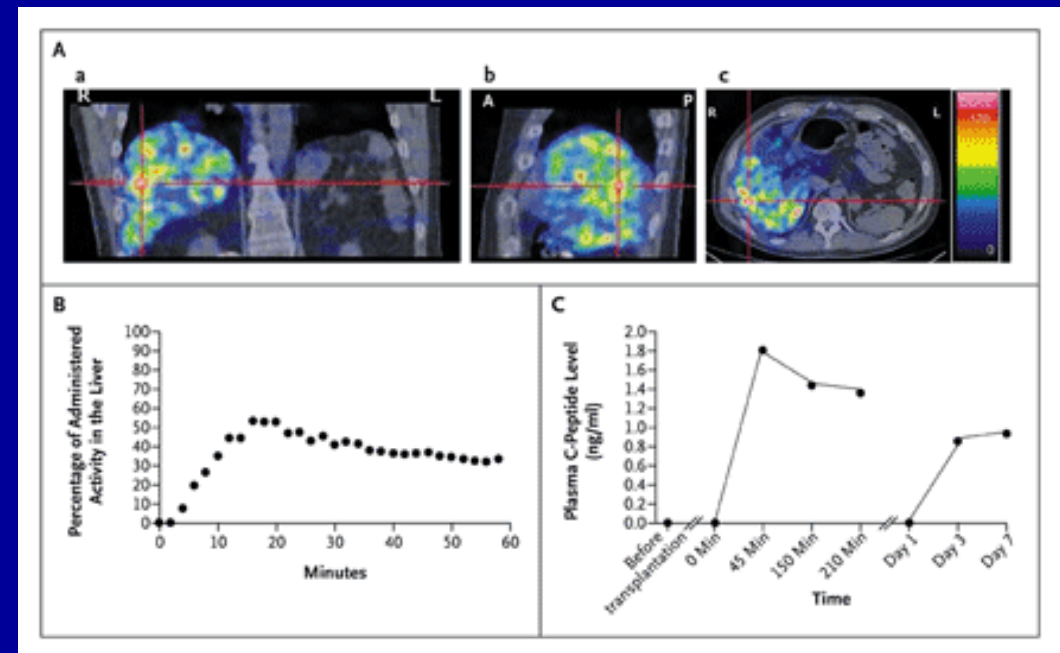
Islet cell transplants: conclusions

- Islet cell transplants are experimental and remain “under development”
- Insulin independence is transient
- Hypoglycaemia control occurs with partial graft function
- Side-effects significant
- Site/experience important in outcome
- HLA sensitization and renal dysfunction [calcineurin inhibitors] currently preclude procedure in potential renal recipients

Islet cell transplants: can they be improved?

- Better islet cell harvests (less donors)*
- Immunosuppression:*
 - Less nephrotoxicity
 - Less islet cell toxicity
 - Less side effects
- Monitoring islets*
- Understanding rejection*
 - Autoimmune/rejection/beta cell exhaustion

- Shipping islets*
- * **Australian Islet Cell Program**



Alternatives

- Stem cells - source
- Xenotransplants - source
- Encapsulated islet cells – evade immune detection
- Non-hepatic engraftment: hepatic islets do not secrete glucagon, exposed to high drug levels
- Closed-loop CSII glucose mediated insulin secretion – non-biological*

Conclusion

- “Islet cell transplantation may be considered an evolving therapy for highly selected patients with severe hypoglycaemia or labile type 1 diabetes, provided all other attempts to stabilize glycaemic control have been exhausted”
- Shapiro AMJ et al. NEJM 2006;355:1318