

Optimising management of patients with Type 1 diabetes: assessing the options for transplantation

James Shaw, Professor of Regenerative Medicine for Diabetes





- Optimised conventional glucose self-management
- Transplantation for renal failure in type 1 diabetes
 - Live donor kidney; simultaneous pancreas kidney; pancreas after kidney
- Need for beta-cell replacement therapy for severe hypoglycaemia
 - Strengths and limitations of deceased donor islet transplantation
- Integration of transplant management into routine diabetes care
 - Mobilising regional NHS islet transplant centres
 - Ultimately to efficiently and effectively deliver stem cell therapy in the UK

Person-centred holistic integrated care for all with diabetes

- Structured education
- Optimised glucose self-monitoring
- Optimised insulin replacement
- Data collection and interpretation

Holistic integrated care for all with diabetes

- Structured education
- Optimised glucose self-monitoring
- Optimised insulin replacement
- Data collection and interpretation
- Transplantation selection, management and support

Renal transplantation is life-saving in diabetes

- Renal replacement therapy with dialysis improves survival
 - Mortality remains 20-fold greater than in general population
- US registry 5-year survival data in people with diabetes
 - 29% on dialysis
 - 75% after deceased kidney transplant
 - 83% after living donor kidney transplant

US Renal Data System. USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2002

Renal transplantation – UK indications

- Gold standard treatment of end stage renal failure
 - Any cause
- Suitable individuals can join the active waiting list
 - Within 6 months of anticipated dialysis date
- Obesity not an absolute contraindication
 - Peri-operative cardiac assessment important
- Diabetes MDTs should provide support in weight optimisation
 - Maximising overall fitness in parallel with glucose self-management

Optimising diabetes self-management in type 1 diabetes – glucose monitoring

Type 1 diabetes in adults: diagnosis and management NICE guideline [NG17] Published: updated: 31/03/22

 Offer adults with type 1 diabetes a choice of real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM) commonly referred to as 'Flash'

DUK-funded trial led by Dr Lala Leelarathna, Manchester 156 people with T1D and sub-optimal glucose

- HbA1c reduced from 72 to 63 mmol/mol
- Less significant hypoglycaemia
- Improved quality of life
- Cost-effective

DUK Professional Conference March 22



Optimising diabetes self-management in type 1 diabetes – continuous glucose monitoring

- Now indicated for all who may benefit (NG17)
- Provides accurate predictive low glucose alarms to patients
 - And others
- Can minimise significant hypoglycaemia
 - Predictive low glucose suspend of pump insulin delivery
- Can help optimise overall glycaemic control
 - Hybrid closed loop pump / CGM systems
 - NHS pilot study pending NICE technology appraisal review



Optimising diabetes self-management in type 1 diabetes – insulin regimens

- Structured education in dose adjustment for all
 - DAFNE; HypoCOMPaSS education (Little et al., Diab Care 2018)
- Multiple Daily Insulin Injections using insulin analogues
 - Novorapid / Humalog; Detemir / Glargine / Degludec
- Continuous Subcutaneous Insulin Infusion pump
 - Indications: disabling hypoglycaemia / high HbA1c
 - Steps to minimise risk of diabetic ketoacidosis
 - Combination with flash / continuous glucose monitoring / hybrid closed loop

Blueprint for a double transplant

To cure Scott Bowles' diabetes and restore his body's ability to filter toxins from his blood, doctors transplanted two organs from an accident victim. The double transplant is an increasingly popular though controversial treatment among the nation's 1 million insulindependent diabetics. About 1,000 such transplants are performed each year in the United States.

How it's done: Doctors attach a new pancreas and kidney to the major blood vessels in the lower abdomen. Scott's defective but somewhat functional pancreas and kidneys are left untouched.

Whole pancreas transplantation

- Offers potential of a 'cure'
 - normal glucose
 - prevention of hypoglycaemia
- Major operation 3% mortality in first year
 - 20% reoperation may lead to graft pancreatectomy
- Requires life-long immunosuppression
- Combined with a kidney transplant







May be stabilised



May improve

May improve

Enhanced quality of life through freedom from insulin Potential for enhanced renal graft and recipient survival

Pancreas transplantation – UK indications

- Simultaneous Pancreas Kidney transplant (SPK)
 - GFR ≤20 ml/min
 - BMI <30 kg/m² / adequate cardiovascular fitness
 - Insulin-treated diabetes (can include monogenic / CF-related / type 2)
- Pancreas After Kidney transplant (PAK)
 - Good renal function after living or deceased renal transplant
- Pancreas Transplant Alone (PTA)
 - Solely for recurrent severe hypoglycaemia
 - Not for recurrent DKA / progressive microvascular complications
- Diabetes MDTs should provide support in weight optimisation



Flatt AJS et al., Diab Med 2020

Pancreas transplantation summary

- Simultaneous pancreas and kidney transplant
 - Early mortality 3% in first year / excellent 1-5 year graft survival
 - Over time associated with improved survival / requires cardiovascular fitness
- Live donor kidney transplant
 - Comparable graft and patient survival to SPK
- Deceased donor kidney transplant
 - Much better outcomes than dialysis
- Pancreas after kidney transplant another option
 - Make the right initial decision re SPK / regalvanise self-management post-KTA
- Pancreas transplant alone
 - Only for life-threatening hypoglycaemia

Impact of conventional therapy on hypoglycaemia

- 100 years' experience with insulin therapy
 - Hypoglycaemia remains limiting factor for optimal control
 - 50% with >15 years' type 1 diabetes experience severe hypo every year
- DCCT 3 fold increase in severe hypoglycaemia
- DAFNE 18% severe hypoglycaemia in first 6 months
- CSII / CGM proportion do not recover awareness
- Exogenous insulin replacement inextricably linked to hypoglycaemia





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The New England Journal of Medicine

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MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., Ellen Toth, M.D., Garth L. Warnock, M.D., Norman M. Kneteman, M.D., and Ray V. Rajotte, Ph.D.

- 7 Type 1 patients with severe hypoglycaemia
 - metabolic instability
- 2-3 donors for each recipient
- Steroid (cyclosporin)-free immunosuppression
- All off insulin at 1 year

Successful but very expensive to set up in all transplant centres 10% insulin independence at 5 years



NCG islet transplant centre

First health service funded programme as an established clinical intervention NHS / NICE: prevention of SH / HbA1c <7%

Minimally invasive procedure





Local anaesthetic and radiological guidance Pain; Haemorrhage <3%; Portal vein thrombosis <3%

Newcastle recipient CGMS





Sensor Modal Day

Medtronic Solutions: CGMS iPro CGMS iPro 2.0A





Impact of islet transplantation on normoglycaemia / hypoglycemia

CGM glucose: 3-10 mmol/L (55-180 mg/dL)

CGM glucose: <3 mmol/L (<55 mg/dL)



C-peptide >200 pmol/L sufficient to prevent hypoglycaemia



Continuous relationship between C-peptide and mean glucose / SD



Brooks AM et al., Diab Care 2015

Severe hypoglycaemia / overall control



<50% sustainable insulin independence despite majority 2 transplants

Instant Blood Mediated Inflammatory Reaction



Smink AM et al., Diabetes 2013

Goal is now reproducible attainment of insulin independence in UK programme

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ORIGINAL ARTICLE

AJT

The impact of islet mass, number of transplants, and time between transplants on graft function in a national islet transplant program

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Indications / contraindications

- Life-threatening recurrent severe hypoglycaemia
 - 'hate hypos' rather than 'hate diabetes'
- C-peptide negative (Mixed Meal Tolerance Test)
 - insulin sensitive (<0.7 units / kg weight / 24 hours)
- Good renal function without macroalbuminuria
 - or stable renal function post-kidney transplant
- Satisfactory cardiac reserve
- No liver hamangiomata / active gall stone disease
- Islet after kidney transplant / simultaneous islet kidney transplant

Immunosuppression / follow-up

- T-cell depleting induction Alemtuzumab
 - Heparin / anti-inflammatory therapy Etanercept
- Tacrolimus monitor trough level (renal function)
 - Mycophenolate Mofetil monitor for neutropenia (FBC)
- Antiviral / antibiotic prophylaxis
 - Valganciclovir / co-trimoxazole
- Graft function monitored by C-peptide
 - Daily insulin dose, HbA1c, severe hypoglycaemia
- Ongoing diabetes care / malignancy screening



Summary of islet activity 1 April 2008 – 31 March 2021



* Transplant list as at 29 February 2020

Unmet needs: sustainable insulin independence from single graft / long term immunosuppression

- Two factors preventing curative therapy for all (30 million)
 - Cannot achieve sustained insulin independence
 - from single minimally invasive procedure
 - Need for toxic life-long immunosuppression
 - to prevent allo- and auto-immune rejection

Immunobarrier encapsulation towards islet transplant without systemic immunosuppression



Hypoxia appears to be main limiting factor Viacyte PEC-direct https://diabetes.diabetesjournals.org/content/ 70/Supplement_1/196-LB



Generation of Functional Human Pancreatic β Cells In Vitro

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Vertex clinical trial in severe hypoglycaemia – with full systemic immunosuppression Dose escalation towards single transplant insulin independence Teratoma risk mitigated by potential to withdraw immunosuppression

Stem cell derived beta-cell replacement therapy



Krentz N et al Lancet D+E 2021

SC / alternative site

Tissue Engineered Product: Scaffold / Islets Adjuvant molecules / gene therapy / cell therapy



Krentz N et al Lancet D+E 2021

Stem cells in clinical practice

- Indications likely to remain around severe hypoglycaemia
 - While long term systemic immunosuppression required
- NHS integrated pancreas and islet transplant programme
 - Provides an equitably accessible network / powerful platform for trials
- Sustainable insulin independence following single elective procedure
 - An exciting attainable goal
 - Strategies for beta-cell replacement without lifelong immunosuppression emerging



- Renal transplantation is life-saving
 - Should be considered pre-dialysis in parallel with optimal diabetes management
- Pancreas transplantation offers insulin independence in type 1 diabetes
 - Ideally provided simultaneously with kidney transplant
- Islet transplantation proven therapy for recurrent severe hypoglycaemia
 - Requires ongoing shared care with the local diabetes MDT and ideally renal MDT
- The UK has established referral / management / follow-up pathways
 - For stem cell-derived beta-cell replacement therapy
- SC therapy for diabetes requires a clinical approach mirroring islet transplant
 - Will soon offer an elective procedure providing sustainable insulin independence
 - Important stepping-stone to a future without insulin or immunosuppression