

The Scotland Wide Islet Transplantation Program



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ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

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Five-Year Follow-Up After Clinical Islet Transplantation

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DIABETES, VOL. 54, JULY 2005

Restoration of Hypoglycaemia Awareness Following Islet Transplantation

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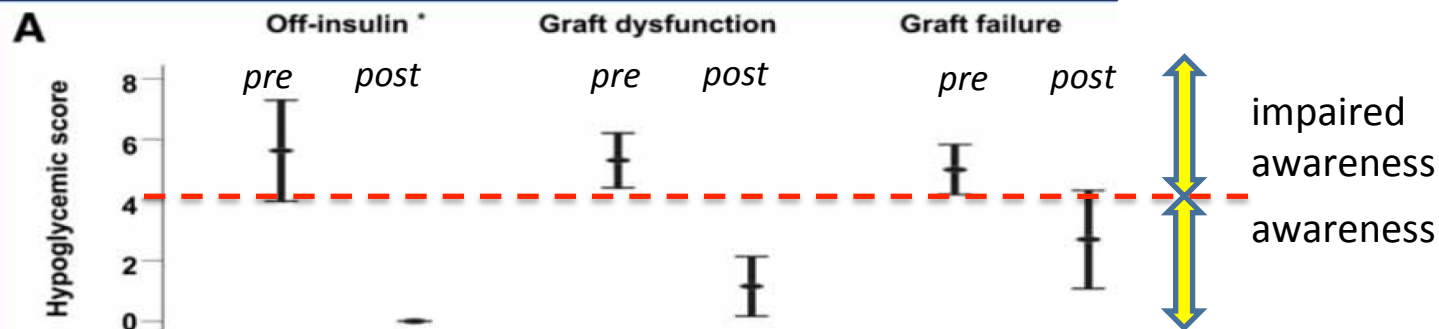
Five-Year Follow-Up After Clinical Islet Transplantation

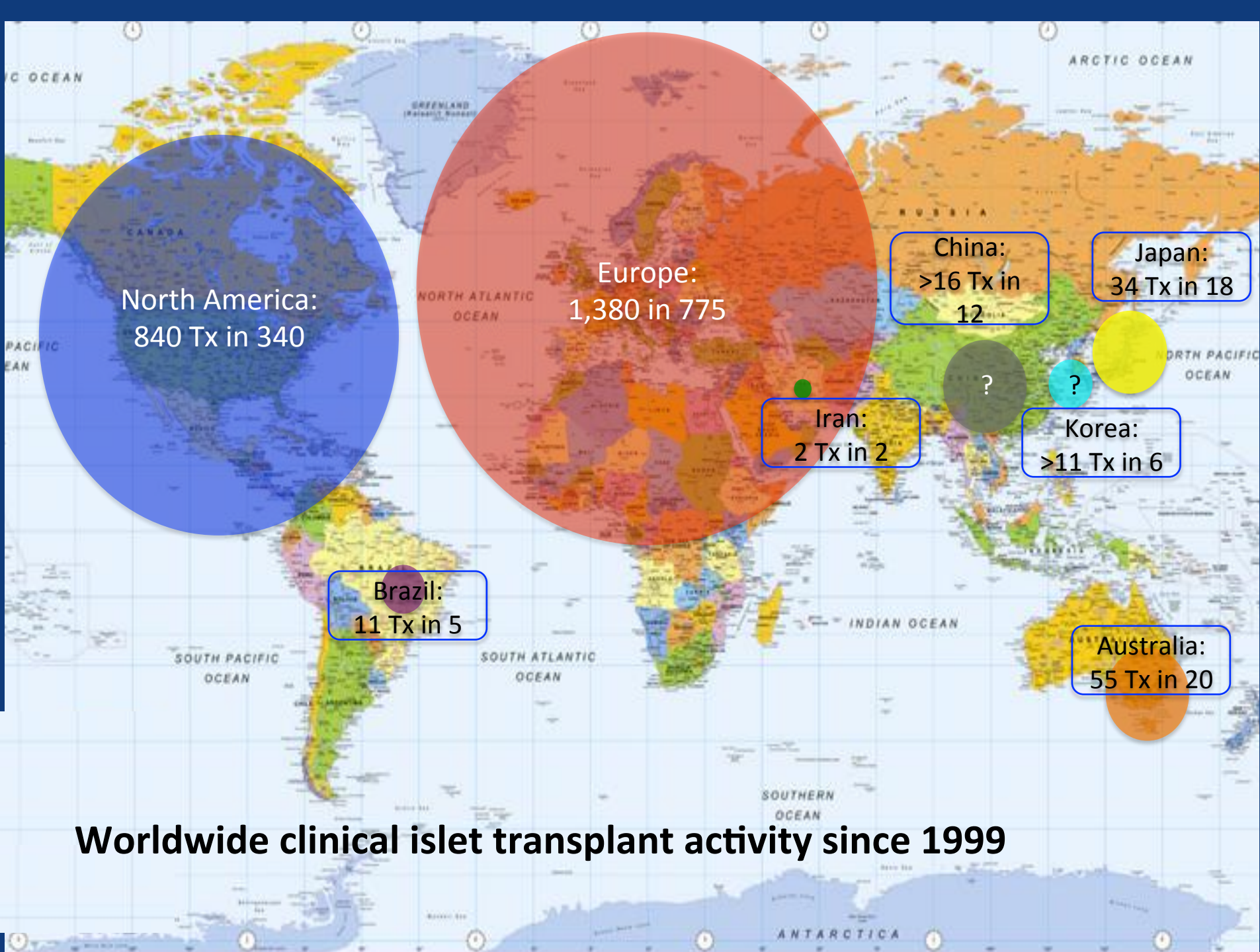
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31 subjects mean duration of diabetes 30 years

Leitao et al *Diabetes* 2008





Worldwide clinical islet transplant activity since 1999

Islet Transplantation in UK: commissioned 1 April 2008

Nationally funded service



UK islet transplant consortium (UKITC)

7 transplant and 3 isolation centres

Scotland wide programme – funded 2009

> 90 patients in UK transplanted to date

Islet Transplantation: Indications in UK

C-peptide negative diabetes

Type 1 diabetes

Post-pancreatectomy

Severe Hypoglycaemia*
with impaired awareness of
hypoglycaemia (IAH)

Renal Transplant with Type 1 diabetes

Islet Transplant after kidney

Glycaemic variability
IAH not necessarily feature

(patients on immunosuppression)

* 1 episode in 1 year (or 2 in 2 years) requiring assistance

Where diabetes control has been intensified and optimised – patients do
NOT need to be on an insulin pump

Islet transplantation

Main aims in UK

- Reduce frequency of hypoglycaemia
- Regain awareness of hypoglycaemia
- Reduce glycaemic variability

Main Contra-indications

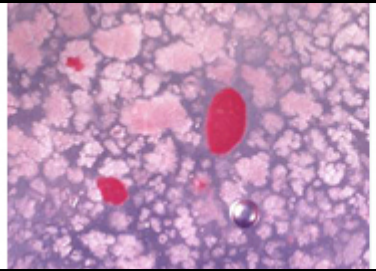
- History of cancer
- Renal impairment with a $\text{eGFR} < 60 \text{ ml/min}$
- Insulin resistance (requiring > 60 units insulin/day to achieve an $\text{HbA1C} < 75 \text{ mmol/mol}$ (9%))
- (obesity relative CI)
- Active proliferative diabetic retinopathy
- Contra-indications to surgical intervention E.g. hypertension, portal hypertension, MI $< 6/12$, bleeding disorder
- *

* Plan for future pregnancy not a contra-indication to islet Tx

Islet transplantation: Edmonton Protocol



Human donor
pancreas



Islet isolation



Purified Islets



Radiology



Vein in liver localised



Islets infused into liver

Islet transplantation

Edmonton protocol followed:

- Select group of patients
- Glucocorticoid free immunosuppression
- Double donor transplants (x2 sequential islet infusions)
- Meticulous surgical and laboratory* preparation
- Immediate transplantation

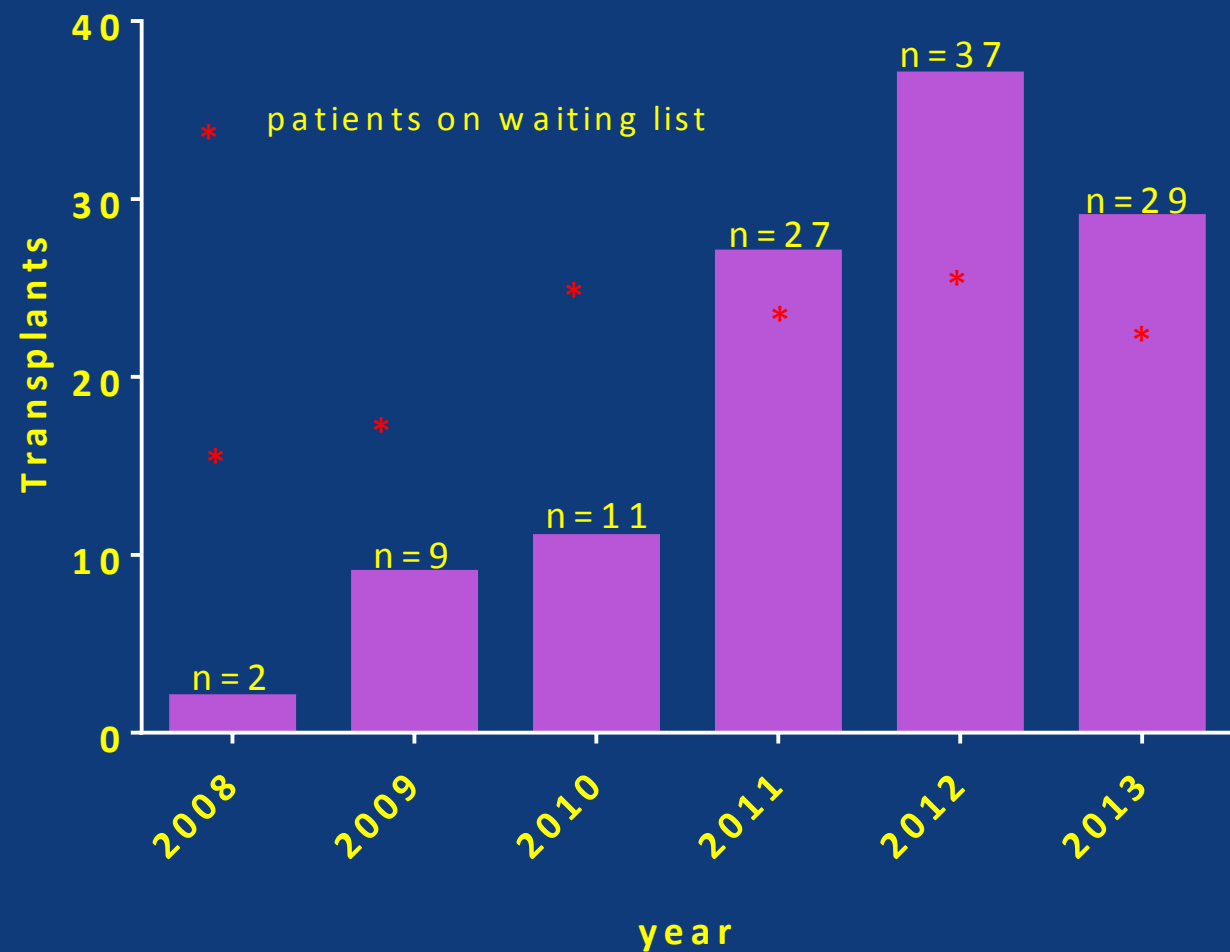
- Alemtuzumab+Etanercept
- Mycophenolate Mofetil
- Tacrolimus
- Valganciclovir (if CMV +ve donor / recipient)
- Cotrimoxazole
- Omeprazole
- Heparin

*Thresholds >200,000 Islet Equivalent Units

Risks and benefits	Islet cell transplant
Death due to the operation or procedure	Less than 1 patient in 100
Operation to open the abdomen	2 patients in 100
Repeat operation on the abdomen	close to zero
Serious surgical complications including colostomy	close to zero
When treatment starts to work	After 12 weeks
Any infection over 6 years	17 patients in 100
Life-threatening infection with long-term clinical effects over 6 years	2 patients in 100
Death due to infection over 6 years	1 patient in 300
Cancer, potentially life-threatening, over 6 years (except skin cancer)	1 patient in 100
Skin cancer including melanoma (often treatable) over six years	8 patients in 100
Severe reduction in kidney function due to anti-rejection medication	Sometimes
Freedom from insulin injections at 1 year	62 patients in 100*
Freedom from insulin injections at 5 years	50-62 patients in 100
Major reduction in severe 'hypos' at 18 months	90-95 patients out of 100
Reduced risk of severe 'hypos' at 5 years	82 patients in 100
Improved HbA1c at 5 years	50-70 patients in 100

Adapted from CITR (<http://www.citrregistry>) information and Shapiro J et al, Diabetes Care 35, July 2012

Summary of islet transplantations in UK: 1 April 2008 – 31 December 2013



Scotland's transplants made up 50% of UK transplants in 2012/3
Not enough donor organs to meet need

PRE-TRANSPLANT ASSESSMENT

Diabetes aspects

Gold score

“Do you know when your hypos are commencing?”

Always aware

Never aware

Awareness

1

2

3

4

5

6

7

Other aspects

- Numbers of hypos requiring assistance
 - Pump vs basal bolus
 - Insulin requirements
 - Dietetics
-
- Note Diabetes Reg responsible for writing up sliding scale and advising on other aspects of diabetes management.
 - Patients immunosuppression and investigations etc are managed by Renal Transplant Physicians.

Dietetics

- Assessment of diabetes management -
 1. Carbohydrate (CHO) counting or not
 2. Dose adjustment – establish insulin to CHO ratio and corrective dose (DAFNE; 500rule/100 rule)
- Arrange follow-up depending on need, eg CHO counting education, consistency in CHO intake, weight management
- Liaise with referring diabetes team
- Complete food diary
- Challenges

Diabetes managment

Pre/peri-transplant

- Patient admitted night before procedure
- CGMS fitted on ward
- Patients on basal bolus insulin regimens – continue basal insulin in all circumstances
- Patients on pumps -disconnect pump but leave cannula in
- Fasted for >4 hours prior to procedure (so if procedure in afternoon can have breakfast plus short acting insulin)
- IV sliding scale commenced approx. 2 hours before procedure. Usual sliding scale protocol followed – detailed in islet protocol
- Sliding scale can come down the next morning. Liaise with islet/diabetes team

Peri-transplant

- 4 hours NBM post transplant
- CHO restriction especially in first 48 - 72 hours aiming for BG levels 4-7mmol – so that islets are not metabolically “stressed”
- 30-35g CHO per meal, 15g CHO snacks
- Usual in patient stay of 2-3 days
- Gradual increase of CHO after discharge
- Note in pump patients insulin for food can be given through pump eg 4 hrs post Tx
- NO IMMEDIATE REDUCTION IN INSULIN REQUIREMENTS SEEN
- Note: TACROLIMUS induces insulin resistance but no immediate increase in insulin requirements noted
- Patients therefore keep same basal rates etc when on ward

Lessons Learned

- More challenging on basal bolus vs. pump to start reducing insulin
- All patients - Insulin reduction approx 2 weeks post transplant
- Need for good understanding of diabetes & CHO counting apparent
- Patient dependency post transplant
- All report improved Quality of Life but anxious
- Most achieving basal insulin independence
- >50% reduction in insulin requirements
- All improved glycaemic control with reduction in HbA1c
- All now have some hypoglycaemic awareness back

Four key measures in UKITC dataset

Graft survival

- 90 minute C-peptide (following a mixed meal) ≥ 50 pmol/l

Annual rate of hypoglycaemic events

- Events at one-year post transplant vs annualised rate while listed

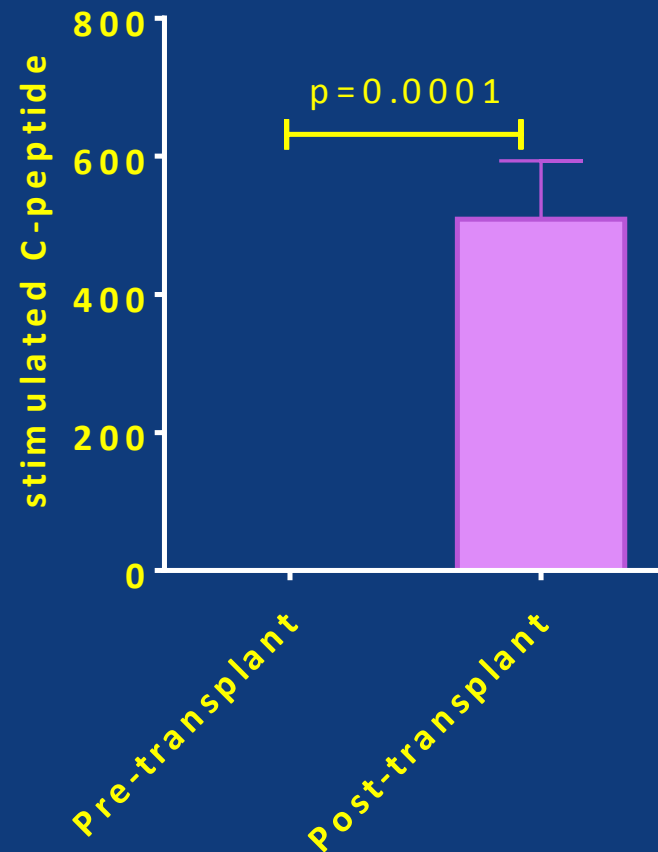
HbA1c (%)

- One-year post transplant vs time of transplant

Insulin dose (units/kg)

- One-year post transplant vs time of transplant

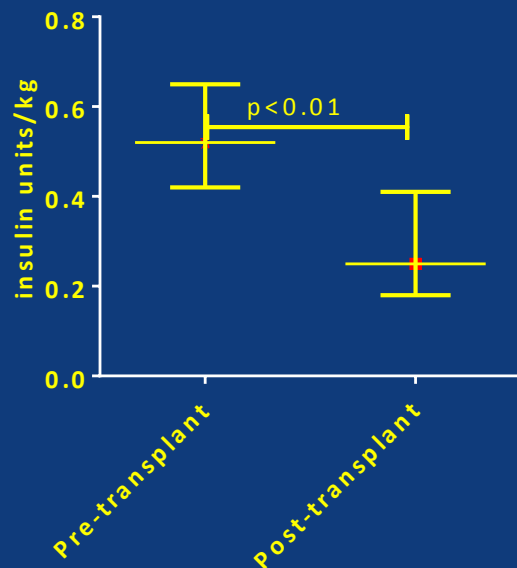
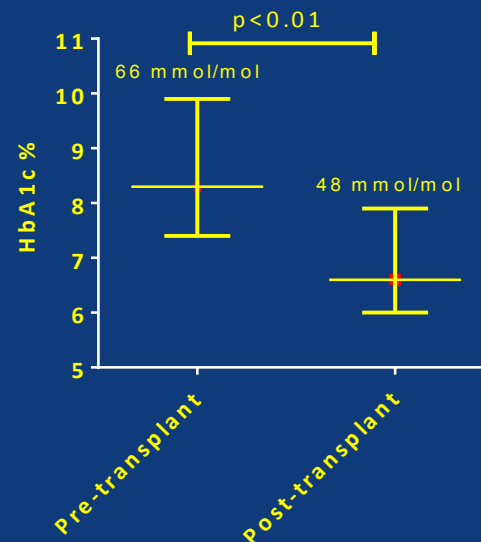
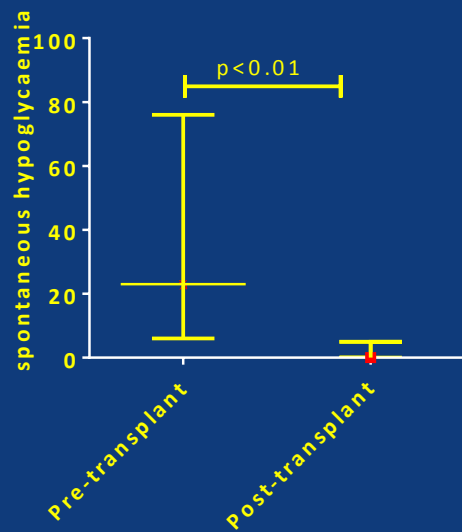
Islet Function Post-Transplantation



18 of 21 patients functioning islet grafts C-peptide >50 nmol/L

Median (Interquartile range)

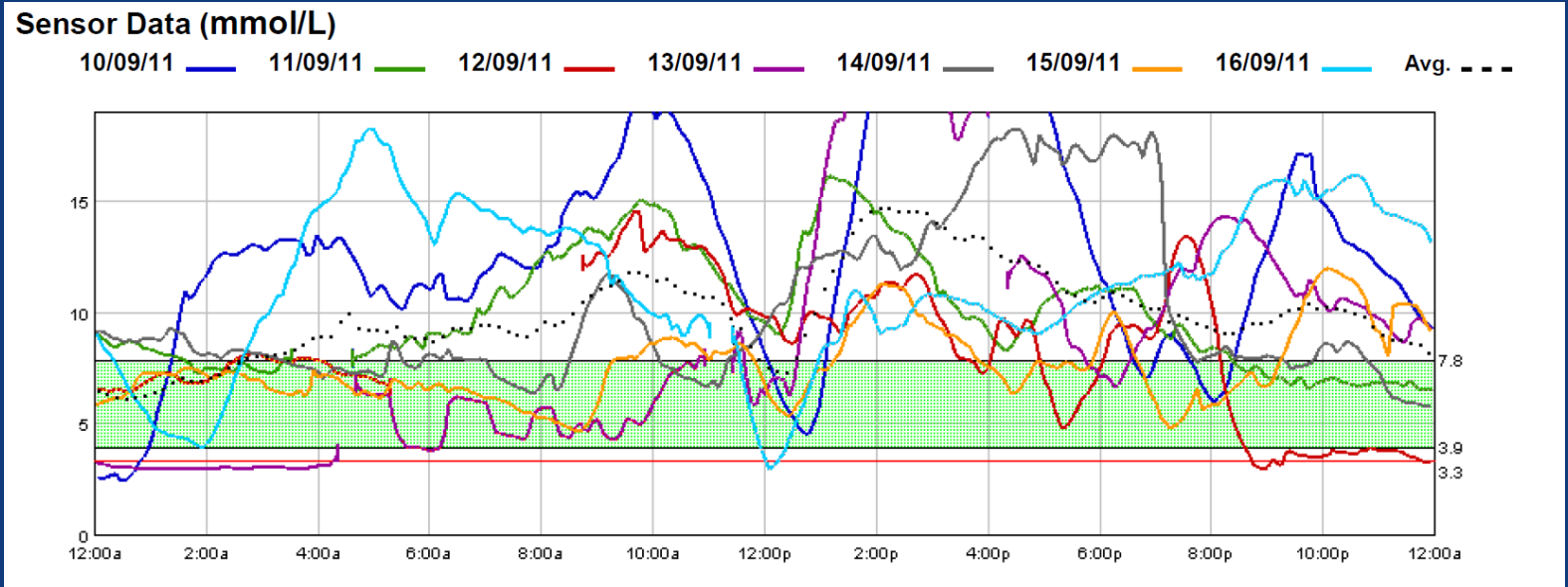
At one year reductions in hypoglycaemia, HbA1c and insulin dose in UKITC



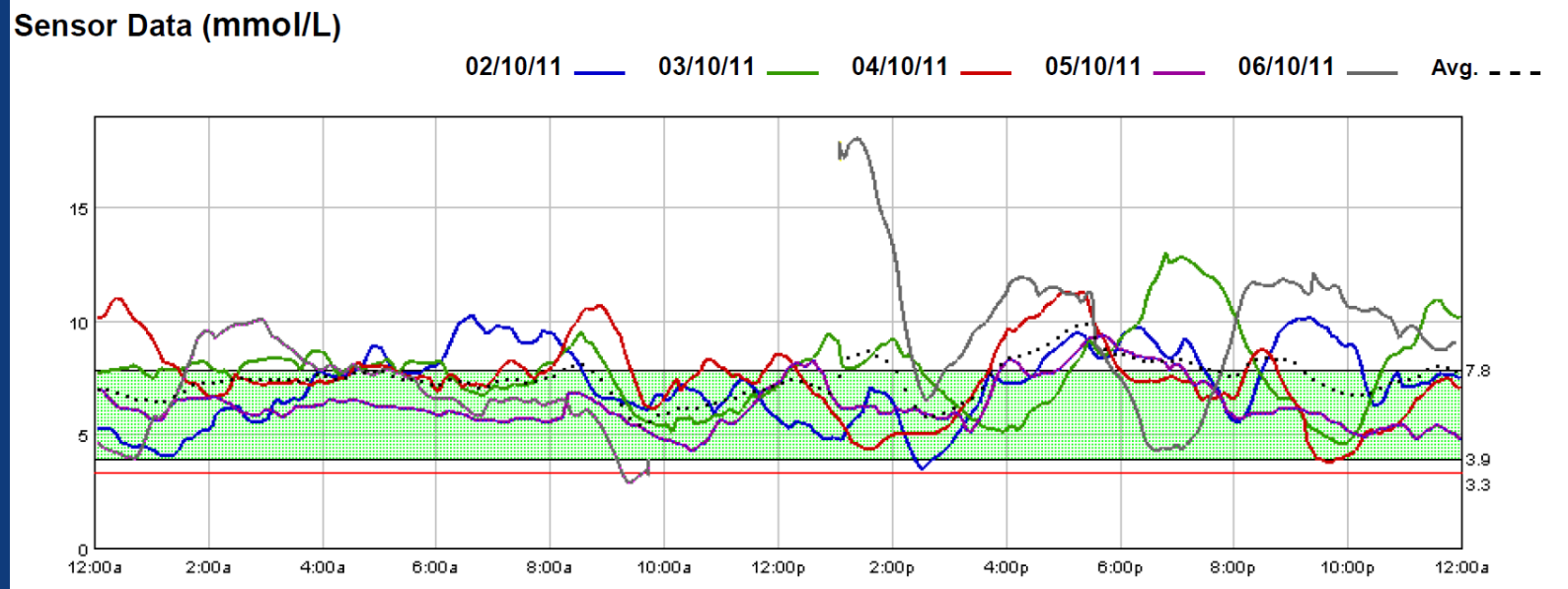
Data from 1 April 2008 – Dec 2013
n=75 patients

Median \pm IQR

Pre Transplant



Post 1st Transplant



Progress

- All patients improved awareness of hypoglycaemia and more independent (4 have regained drivers license)
- 70% have achieved insulin independence for a period of time
- All with decreased insulin requirements
- 1 patient has lost graft function (c-peptide <50 pmol/l)
- 1 patient with severe neutropenia requiring GCSF
- 1 patient with gastritis
- No surgical complications

- Qualitative studies under way
- Diabetes related end-points recorded



Keith, 54 year old patient:

"I have my (hypoglycaemic) awareness back and resumed my love of running. My life is normal again, it's nothing short of a miracle..."



Paul, 40 year old patient:

"I can now feel my hypoglycaemic attacks and I can do things independently once again. I can travel around on my own and have regained my drivers license.."



Acknowledgements

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John Drain



Radiologists

James Gordon-Smith

Hamish Ireland

Neil Masson

Department of Transplantation

Department of Diabetes

Department of Renal Medicine

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Organ Donation and Transplantation

