Living Cell Technologies Limited

ACN: 104 028 042
ASX: LCT
OTCQX: LVCLY

ASX ANNOUNCEMENT

Update on clinical trials of encapsulated pig islets.

16 November 2015 – Sydney, Australia & Auckland, New Zealand - Today at the Joint Congress of the International Xenotransplantation Association (IXA) and International Pancreas and Transplant Association (IPITA) and the Cell Transplant Society (CTS) in Melbourne, Professor Shinichi Matsumoto, Chief Scientific Advisor, Otsuka Pharmaceutical Factory, Inc. (OPF) gave the attached presentation entitled "Clinical trial of encapsulated neonatal porcine islet xenotransplantation". The presentation includes a review and update of Diatranz Otsuka Limited's clinical trials of DIABECELL®, a cell therapy for type 1 diabetes.

LCT and OPF each hold a 50% interest in Diatranz Otsuka Limited which has licensed OPF to further develop DIABECELL in USA.

– Ends –

For further information: www.lctglobal.com

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About Living Cell Technologies

Living Cell Technologies Limited (LCT) is an Australasian biotechnology company improving the wellbeing of people with serious diseases worldwide by discovering, developing and commercialising regenerative treatments which restore function using naturally occurring cells.

LCT's lead product NTCELL® is an alginate coated capsule containing clusters of neonatal porcine choroid plexus cells. After transplantation NTCELL functions as a biological factory producing factors to promote new central nervous system growth and repair disease induced nerve degeneration.

The Phase I/IIa NTCELL clinical trial in New Zealand for the treatment of Parkinson's disease met the primary endpoint of safety and showed clinical efficacy improvements. These encouraging results presented at the World Congress of Movement Disorders and Parkinson's Disease, San Diego in June

2015 have been used to design a larger Phase IIb trial to evaluate its potential as a disease-modifying treatment for patients with Parkinson's disease.

NTCELL has the potential to be used in a number of other central nervous system indications such as Huntington's, Alzheimer's and motor neurone diseases.

LCT's proprietary encapsulation technology, IMMUPEL™, allows cell therapies to be used without the need for co-treatment with drugs that suppress the immune system.

LCT is listed on the Australian (ASX: LCT) and US (OTCQX: LVCLY) stock exchanges. The company is incorporated in Australia, with its operations based in New Zealand.

For more information visit www.lctglobal.com or follow @lctglobal on Twitter

Forward-looking statements

This document may contain certain forward-looking statements, relating to LCT's business, which can be identified by the use of forward-looking terminology such as "promising," "plans," "anticipated," "will," "project," "believe," "forecast," "expected," "estimated," "targeting," "aiming," "set to," "potential," "seeking to," "goal," "could provide," "intends," "is being developed," "could be," "on track," or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other health authorities' requirements regarding any one or more product candidates nor can there be any assurance that such product candidates will be approved by any health authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialisation of the product candidates could be affected by, among other things, unexpected clinical trial results, including additional analysis of existing clinical data, and new clinical data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialise, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected. LCT is providing this information and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise.

Otsuka Pharmaceutical Factory, Inc.
Otsuka

Diatranz Otsuka Ltd

Clinical trial of encapsulated neonatal porcine islet xenotransplantation

Shinichi Matsumoto

Otsuka Pharmaceutical Factory Inc
Diatranz Otsuka Ltd

Nov 16 2015 IPITA-IXA-CTS Melbourne

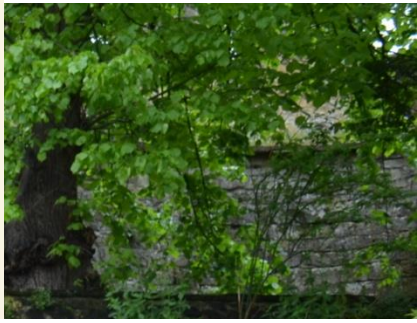
☆ Current status of allogeneic islet transplantation and its limitation especially donor shortage

☆ Advantage and disadvantage of islet xenotransplantation using porcine islets

☆ Clinical outcomes of encapsulated neonatal porcine islet xenotransplantation

☆ Future direction of porcine islet xenotransplantation

IPITA OPINION LEADERS CONSENSUS MEETING ON BETA CELL REPLACEMENT



Oxford, United Kingdom
May 7-9, 2014

ipita | international pancreas & islet transplant association

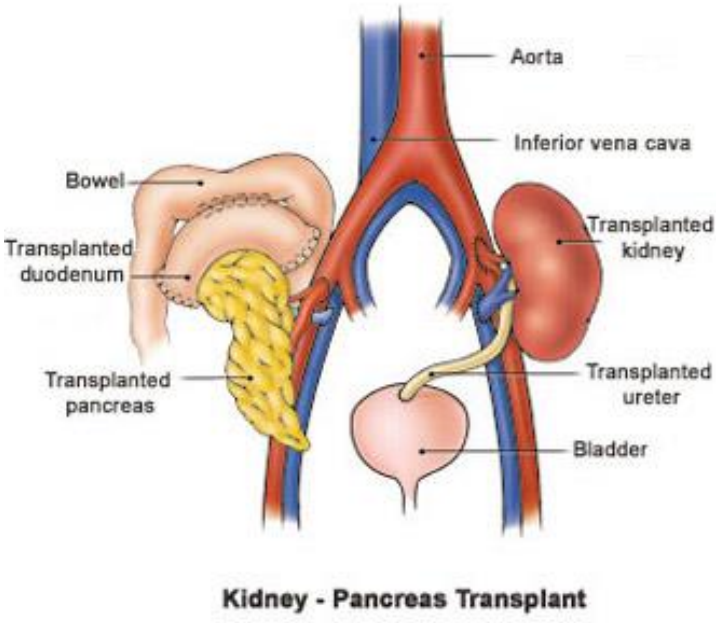
a section of The Transplantation Society

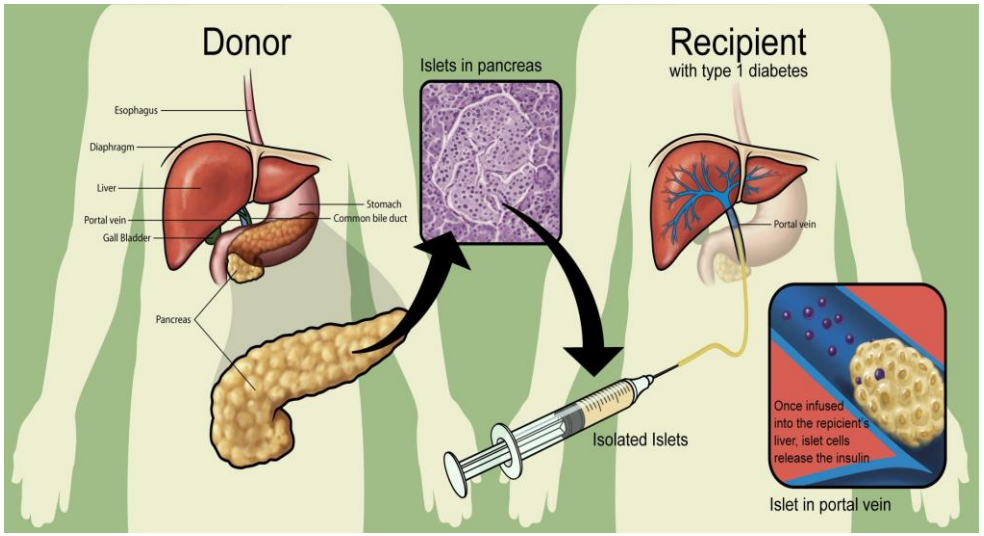
Rationale for beta cell replacements

- 15 to 20 million people worldwide suffer from type 1 diabetes (T1D). WHO. Diabetes. 2010
- 12.5 % of patients with T1D for >20 yrs are unaware of hypoglycemia. Pedersen-Bjergaard et al., DMRR 2009
- 7 to 10% of all patients with T1D die from complications of hypoglycemia. Reviewed by Cryer PE, *Diabetes* 2011
- The effectiveness of human pancreas and islet transplantation in restoring protection from severe hypoglycemia is unmatched by any other therapy.
- However, these therapies are at best available to 0.1% of patients with T1D.

Beta Cell Replacement Therapy

Pancreas and Islet Transplantation



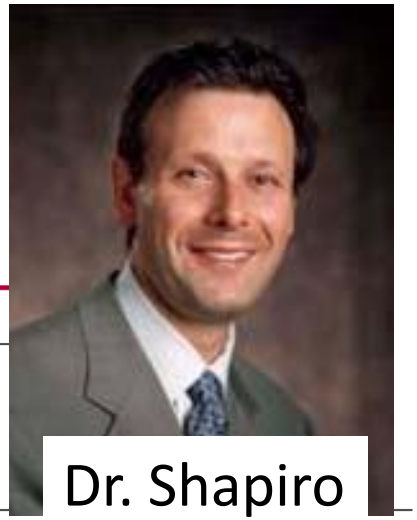


Pancreas transplantation
(Major Surgical Procedure)

Islet Transplantation
(Cell infusion under local anesthesia)

The New England Journal of Medicine

VOLUME 343 JULY 27, 2000



Dr. Shapiro

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES 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.,

Edmonton Protocol

Insulin free at 1 year after islet transplantations

Cell infusion can be the replacement of major surgery

Allogeneic Islet Transplantation

A recent multicenter prospective phase 3 study demonstrated that:

1) Islets can be manufactured reproducibly at multiple sites using a common manufacturing process

2) Independence from exogenous insulin can be achieved in about half of islet recipients at 1 year from infusion with 1 or 2 infusions needed

3) Glycemic control is excellent even when insulin independence is not achieved

4) Hypoglycemia unawareness is treated effectively by islet transplant with associated freedom from severe hypoglycemic events

Bartlett et al. Report from IPITA-TTS Opinion Leaders meeting on the Future of Beta Cell Replacement. *Transplantation in press*

Remaining issues of islet transplantation

1. Donor shortage
2. Necessity of immunosuppressant

Alleviate donor shortage

Successful Islet Transplantation from Nonheartbeating Donor Pancreata Using Modified Ricordi Islet Isolation Method

(Transplantation 2006)

Shinichi Matsumoto,[1,7] Teru Okitsu,[2] Yasuhiro Iwanaga,[2] Hirofumi Noguchi,[2] Hideo Nagata,[2] Yukihide Yonekawa,[2] Yuichiro Yamada,[3] Kazuhito Fukuda,[3] Toshiya Shibata,[4] Yasunari Kasai,[5] Taira Maekawa,[5] Hiromi Wada,[6] Takayuki Nakamura,[6] and Koichi Tanaka[2]

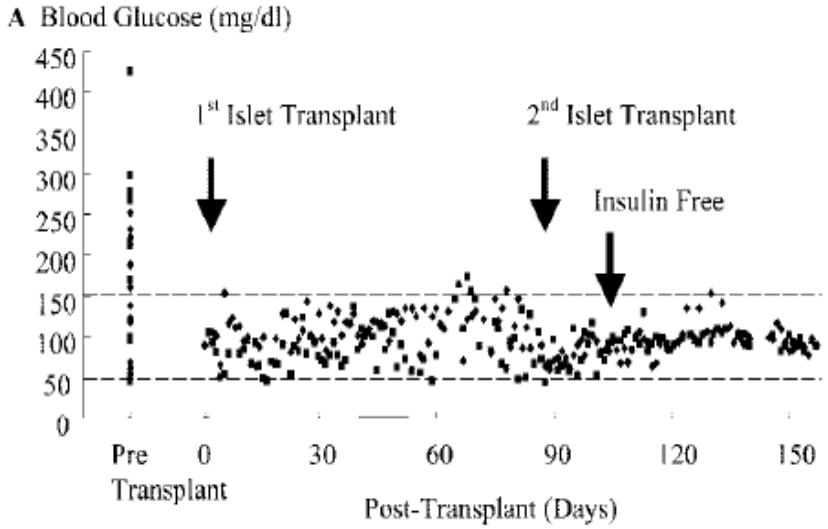
The First Japanese Islet Transplantation

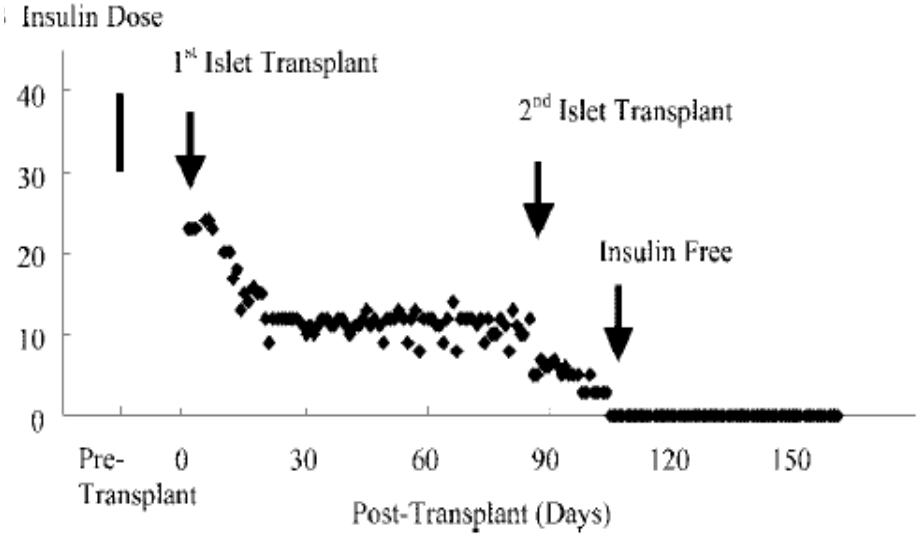
April 2004 Kyoto Japan

Successful Islet Transplantation from Nonheartbeating Donor Pancreata Using Modified Ricordi Islet Isolation Method

(Transplantation 2006)

Shinichi Matsumoto,[1,7] Teru Okitsu,[2] Yasuhiro Iwanaga,[2] Hirofumi Noguchi,[2] Hideo Nagata,[2] Yukihide Yonekawa,[2] Yuichiro Yamada,[3] Kazuhito Fukuda,[3] Toshiya Shibata,[4] Yasunari Kasai,[5] Taira Maekawa,[5] Hiromi Wada,[6] Takayuki Nakamura,[6] and Koichi Tanaka[2]

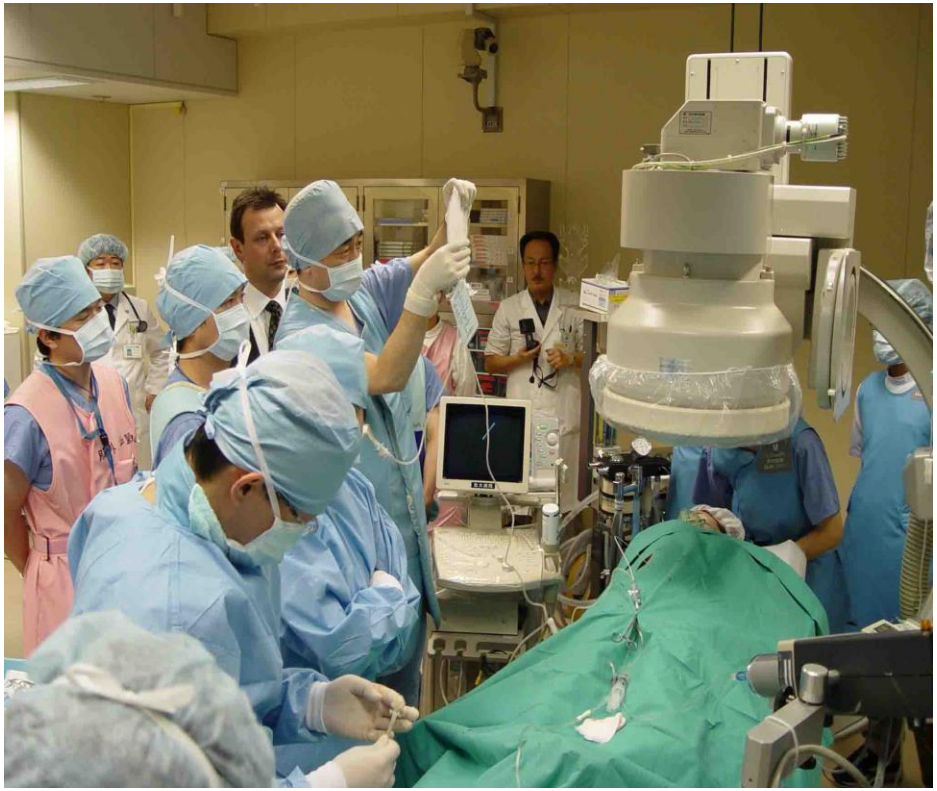




Insulin independence after living-donor distal pancreatectomy and islet allotransplantation

Lancet 2005; 365: 1642–44
Published online April 19, 2005
10.1016/S0140-6736(05)66383-0

Shinichi Matsumoto, Teru Okitsu, Yasuhiro Iwanaga, Hirofum Katsushi Tsukiyama, Haruhiko Suzuki, Yukiko Kawasaki, Maki A M James Shapiro, Koichi Tanaka



Kyoto University Hospital Jan 19th 2005

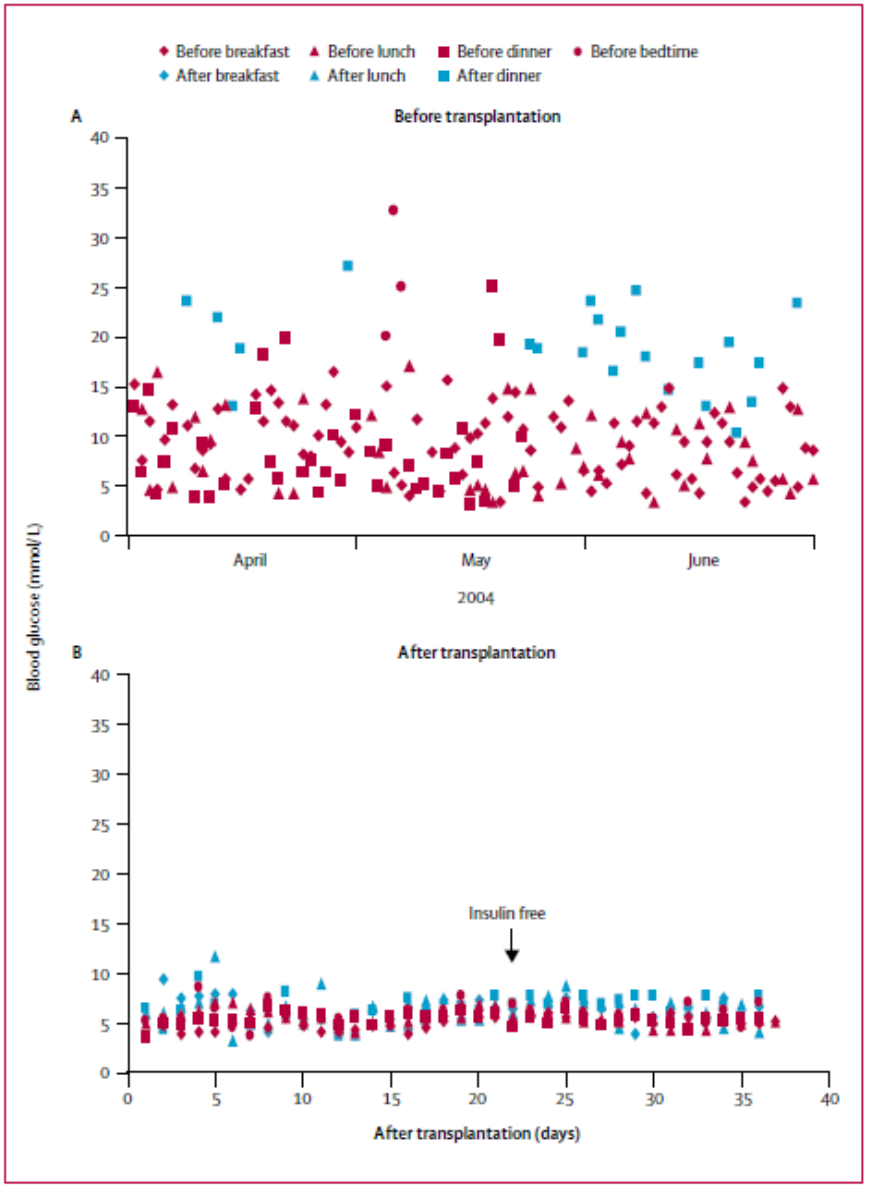


Figure 1: Daily blood glucose before and after islet transplantation

Improving success rate of islet isolation

Cell Transplantation, Vol. 19, pp. 291–297, 2010
Printed in the USA.

0963-6897/10 $90.00 + .00
DOI: 10.3727/096368909X481773
E-ISSN 1555-3892
www.cognizantcommunication.com

Seven Consecutive Successful Clinical Islet Isolations With Pancreatic Ductal Injection

Shinichi Matsumoto,*[1] Hirofumi Noguichi,*[1] Masayuki Shimoda,† Tetsuya Ikemoto,* Bashoo Naziruddin,† Andrew Jackson,†‡ Yoshiko Tamura,† Greg Olson,† Yasutaka Fujita,* Daisuke Chujo,§ Morihito Takita,* Naoya Kobayashi,¶ Nicholas Onaca,† and Marlon Levy*†

Group	Success Isolation	Success Transplant
Ductal Preservation	7/7 (100%)	6/7 (86 %)
Standard	3/8 (37.5%)	2/8 (25 %)
P value	<0.03	<0.05

Single donor islet transplantation

Table 3. Single-donor islet protocols

Center	Approach	Year	Reference
Minnesota	Anti-CD3 + etanercept	2005	Hering *et al.* [35]
Pennsylvania	Edmonton-like	2003	Markmann *et al.* [254]
Emory	Efalizumab + MMF	2010	Turgeon *et al.* [209]
San Francisco	ATG + efalizumab + SRL or MMF	2010	Posselt *et al.* [255]
San Francisco	ATG + belatacept + SRL or MMF	2010	Posselt *et al.* [38]
Edmonton	Peritransplant insulin + heparin	2010	Koh *et al.* [99]
Kyoto	Living donor islet transplant	2005	Matsumoto *et al.* [220]
Baylor	ATG + anakinra + etanercept	2011	Matsumoto *et al.* [256]
Vancouver	Exenatide	2007	Ghofaili *et al.* [189]
Miami	Exenatide	2009	Faradji *et al.* [184]
UIC	Exenatide	2008	Gangemi *et al.* [190]

Legend: ATG – antithymocyte globulin, MMF – mycophenolate mofetil, SRL – sirolimus, UIC – University of Illinois at Chicago.

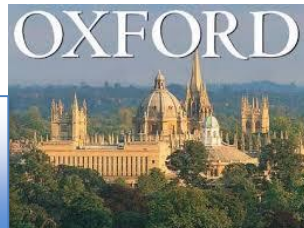
Rationale for pig islets

Availability of
Plenty, Potent, Safe Islets

- Unlimited and on-demand supply
- Consistently high quality of islets from healthy pigs
- Designated pathogen-free pigs are safer islet donors than deceased human donors

Possibility of
Less Immunosuppression

- Pig islets could be less susceptible to autoreactive, MHC-restricted CD8 Tm cells
- Genetic modification of source pigs presents real opportunities for minimizing recipient immunosuppress.



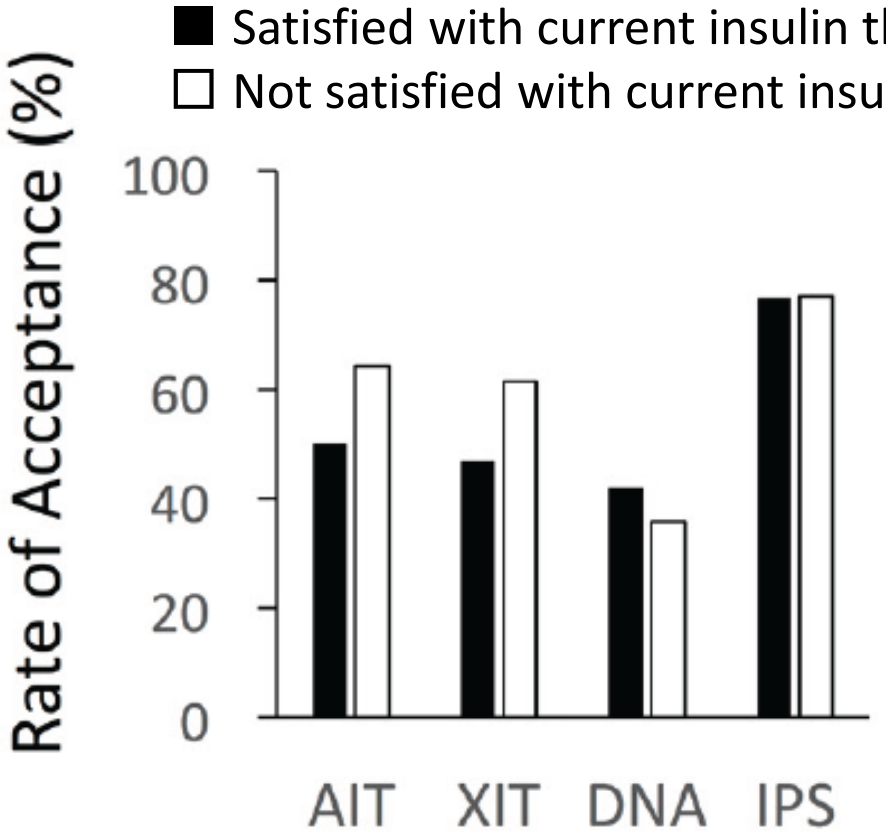
Patients' acceptance of porcine islet xenotransplant

Questionnaire Survey of Patients with Type-1 Diabetes Mellitus and their Family Members on the Acceptance of Newly Emerging Therapies

Masayuki Shimoda* and Shinichi Matsumoto

Islet Cell Transplantation Project, Diabetes Research Center, Research Institute of National Center for Global Health and Medicine, Tokyo, Japan

(J Diabetes Metab in press)



AIT (Allogeneic islet Tx)
XIT (Xenogeneic islet Tx)
DNA (DNA vaccination)
iPS (iPS cell Tx)

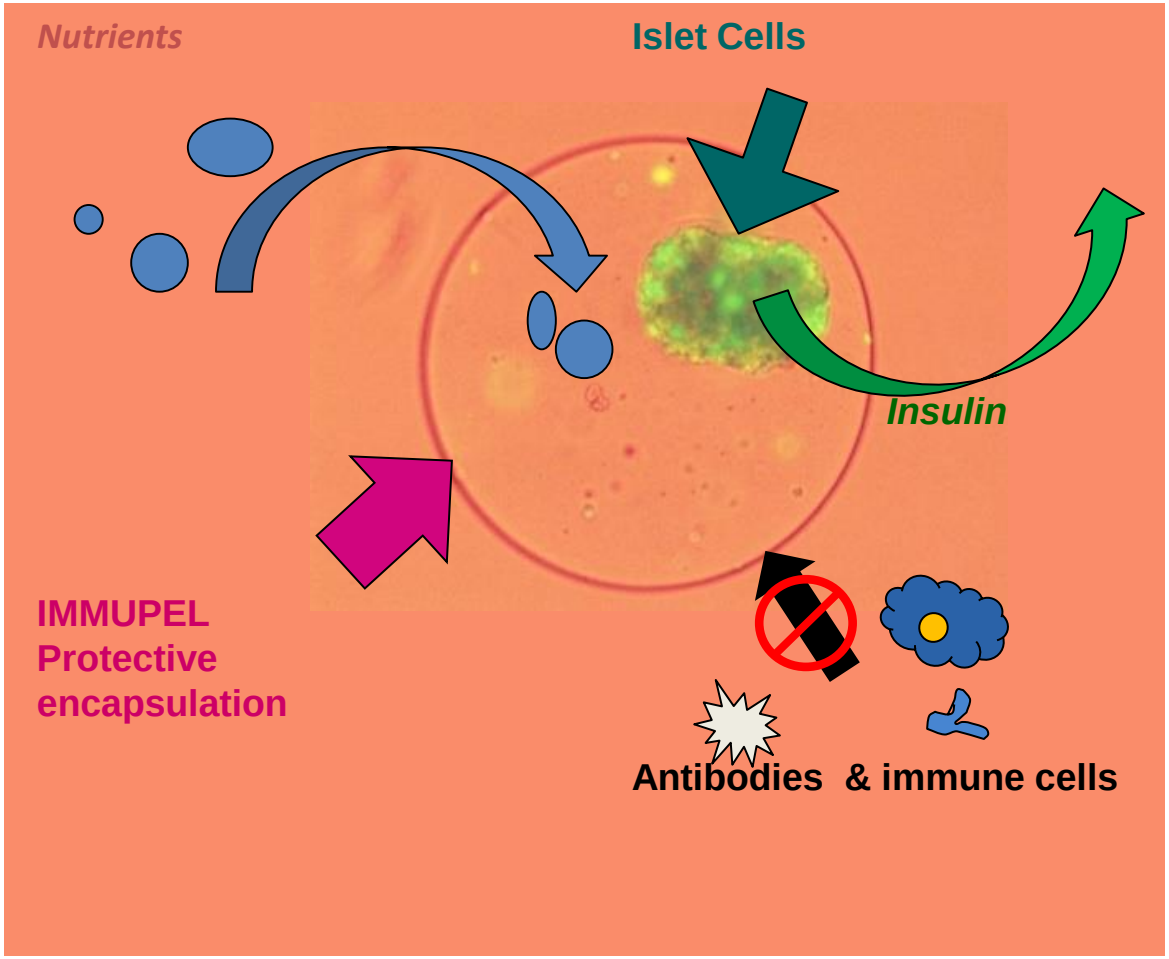
Remaining issues of islet transplantation

1. Donor shortage
2. Necessity of immunosuppressant

Encapsulated Porcine Islet Xenotransplantation

DIABECELL®

Islet Cell Implant Without Immunosuppression



Capsule also provides suitable environment

New Zealand Clinical Trial

Clinical Porcine Islet Xenotransplantation Under Comprehensive Regulation

S. Matsumoto[a,*], P. Tan[b], J. Baker[c], K. Durbin[b], M. Tomiya[a], K. Azuma[a], M. Doi[a], and R.B. Elliott[b]

[a]Otsuka Pharmaceutical Factory, Naruto, Japan; [b]Living Cell Technologies, Auckland, New Zealand; [c]Centre for Clinical Research and Effective Practice, Middlemore Hospital, Auckland, New Zealand

(Transplant Proc. 2014)

Patient Characteristics in Each group (mean ± SE)

	N	Transplanted Islet Yield (IEQ)	Age (Y)	BMI (Kg/m2)	Duration of T1DM (Y)
1 (5K)	4	5,057 ± 84	51.0 ± 6.0	24.4 ± 2.7	18.8 ± 3.1
2 (10K)	4	10,416 ± 613	50.8 ± 4.1	23.2 ± 1.4	24.0 ± 4.8
3 (15K)	4	14,456 ± 334	53.3 ± 3.7	26.2 ± 1.3	17.5 ± 4.1
4 (20K)	2	19,822 ± 716	59.0 ± 4.1	28.7 ± 1.0	28.5 ± 2.0

Serious Adverse Events

4 Serious Adverse Events

★ Post procedural discomfort

★ Anxiety

★ Depressed mood

★ Hypersensitivity reaction

☆ No PERV or Porcine related infection

Matsumoto S et al. Transplant Proc. 2014

Number with unaware hypoglycemia at baseline (-4 to -1 week) and at 1 year (49-52 week)

Group	Baseline	1 year after Tx
1 (5K) (N=4)	11.5 ± 4.2	4.8 ± 1.5
2 (10K) (N=4)	13.0 ± 4.4	2.8 ± 2.1
3 (15K) (N=4)	9.8 ±7.5	9.0 ± 4.0
4 (20K) (N=4)	24.5±8.5	14.0 ± 8.0

Matsumoto S et al. Transplant Proc. 2014

HbA1c and daily insulin dose at baseline and at 1 year after transplantation

	HbA1c (%)		Daily insulin dose (U)	
Group	Baseline	1 year after Tx	Baseline	1 year after Tx
1	7.38 ± 0.43	7.35 ± 0.51	49.5 ± 37.4	37.4 ± 6.2
2	7.65 ± 0.21	7.63 ± 0.22	31.1 ± 5.2	29.5 ± 3.4
3	7.53 ±0.28	7.80 ± 0.37	41.8 ± 7.0	37.9 ± 4.1
4	7.30±0.16	6.6	56.6 ± 1.9	59.9± 4.5

Matsumoto S et al. Transplant Proc. 2014

Transplant Estimated Function (TEF)

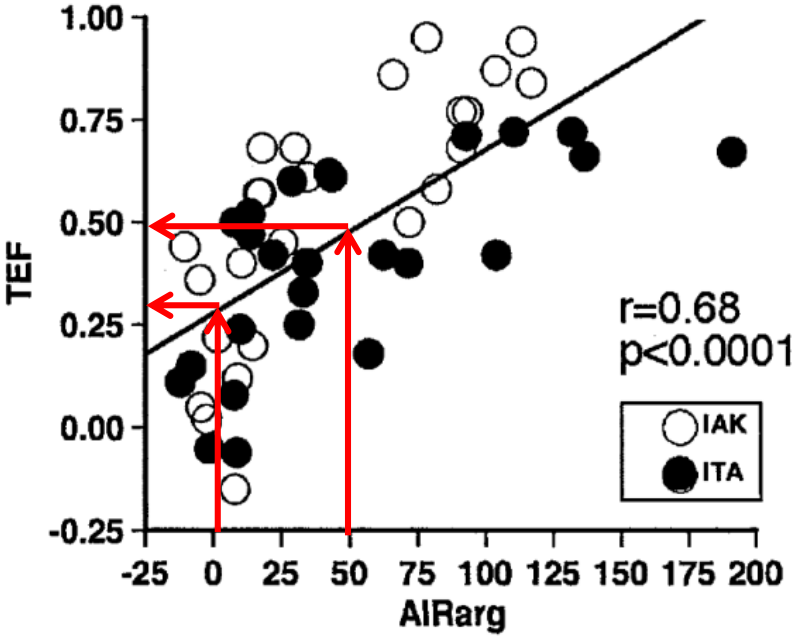
TEF score can be calculated with daily insulin dose/kg and HbA1c

$$TEF = \left[DIR_{pre\text{-}tx} + \frac{A1C_{pre\text{-}tx}}{5.43} \right] - \left[DIR + \frac{A1C}{5.43} \right]$$

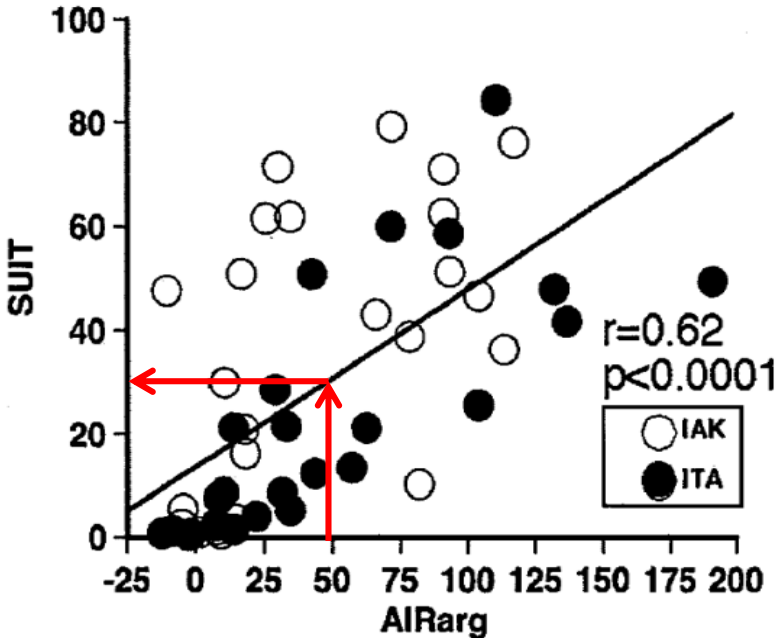
(Caumo et al. Transplantation 2011,92, 815-821)

Correlation between Acute Insulin Response and TEF score and SUITO index

TEF score



SUITO index



TEF = 0.3 is minimum for positive C-peptide level

TEF = 0.5 is similar to SUITO = 30 (reflects insulin free)

(Caumo et al. Transplantation 2011,92, 815-821)

TEF score at 1 year after transplantation

Group	1 year after Tx
1 (5K) (N=4)	0.17 ± 0.15*
2 (10K) (N=4)	0.02 ± 0.03
3 (15K) (N=4)	-0.01 ± 0.05
4 (20K) (N=4)	0.08

* 1 patient showed TEF = 0.58

Matsumoto S et al. Transplant Proc. 2014

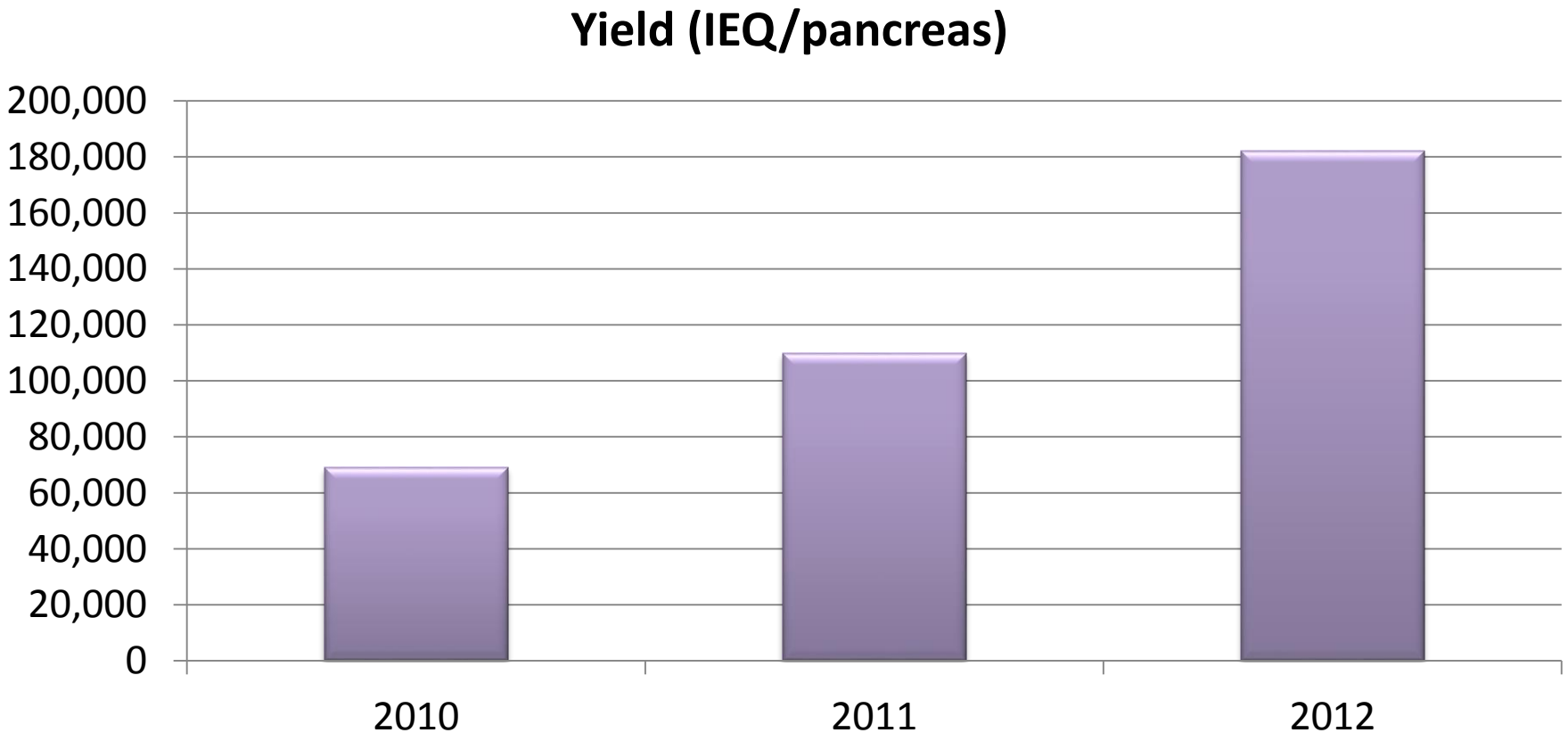
Lessons from NZ trial

- ☆ Safe procedure
- ☆ No infectious issue so far
- ★ Efficacy is not stable
- ● High doses are not more effective than low dose

For the next trial

- ○ Improved quality of islets
- ○ Low dose x 2

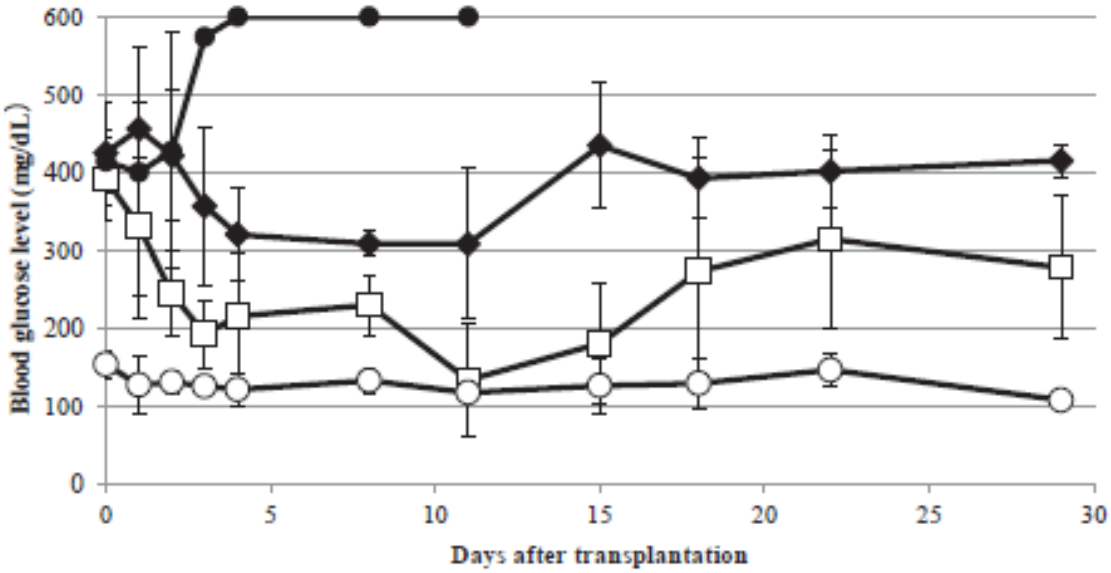
Average Islet Yield per one piglet with islet isolation improvement



(Matsumoto S, et al. IPITA 2013)

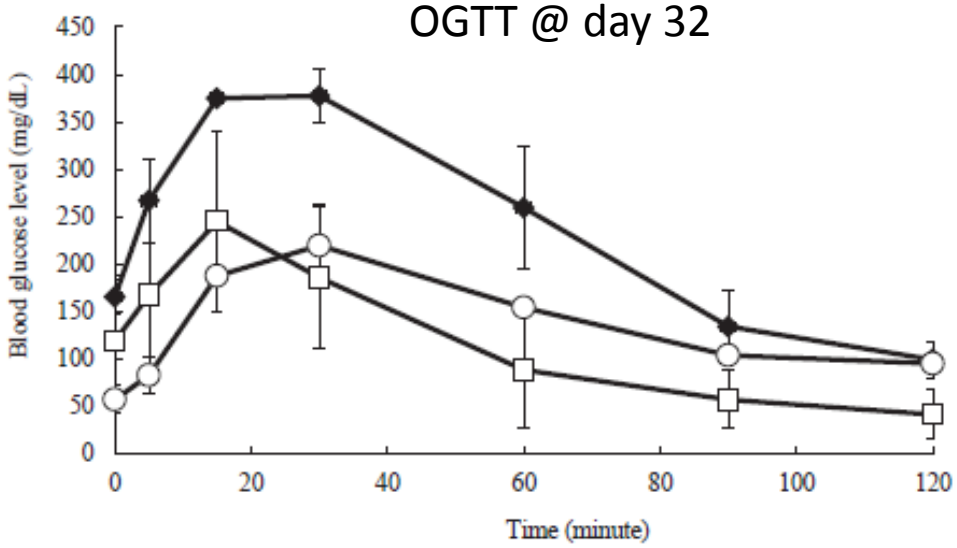
In vivo viability assay using diabetic mice for encapsulated neonatal porcine islets

Daily non-fasting blood glucose



- STZ only (diabetic control)
- Marginal dose
- Sufficient dose
- Healthy control

OGTT @ day 32



Transplantation Proceedings, 46, 1992–1995 (2014)

Diatranz Otsuka Ltd

Interim Analysis:
Data still under analysis

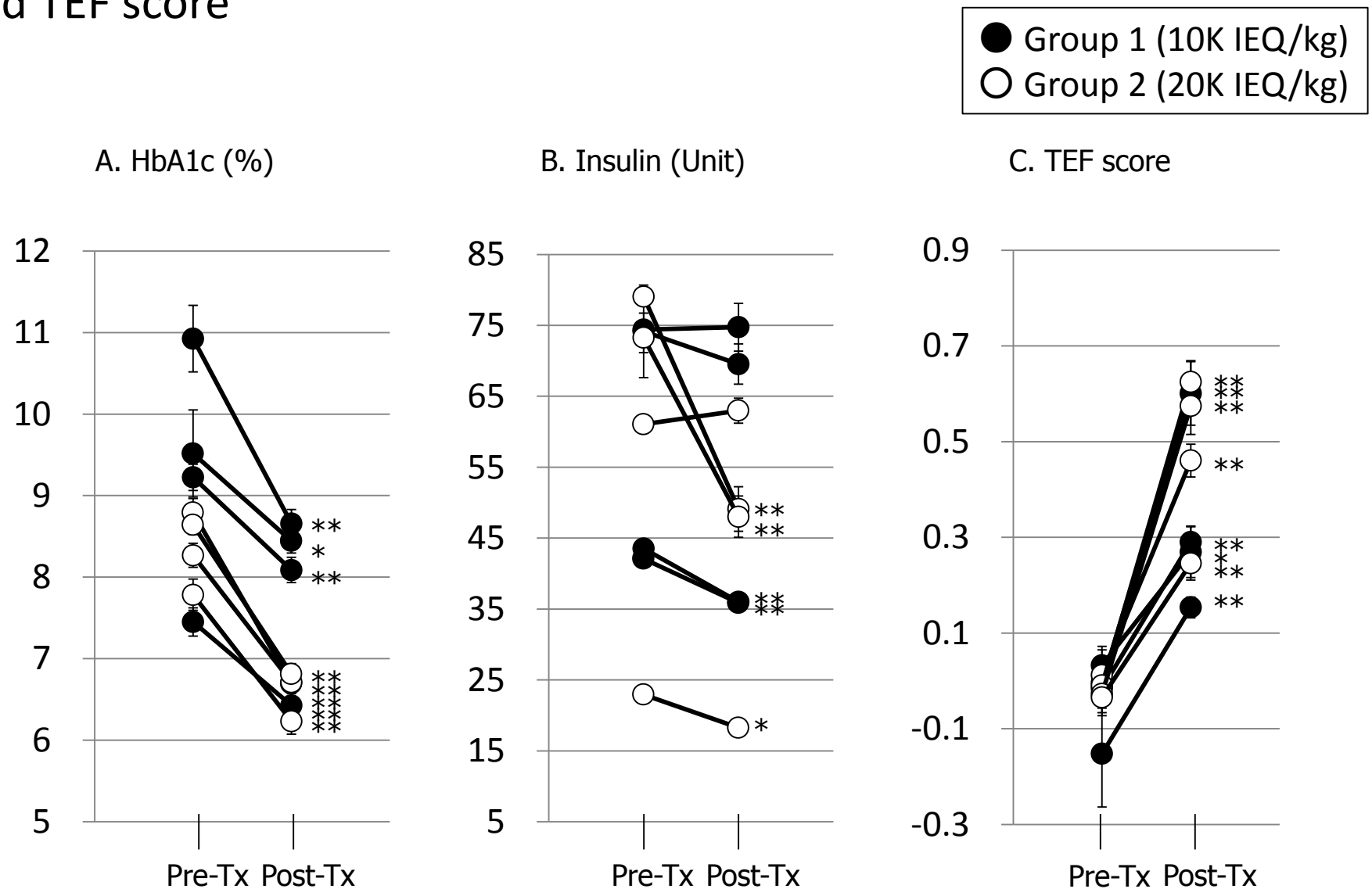
Argentine Trial DIA09

5000IEQ/kg x 2 （N=4)
10000IEQ/kg x 2 （N=4)

Patients Characteristics

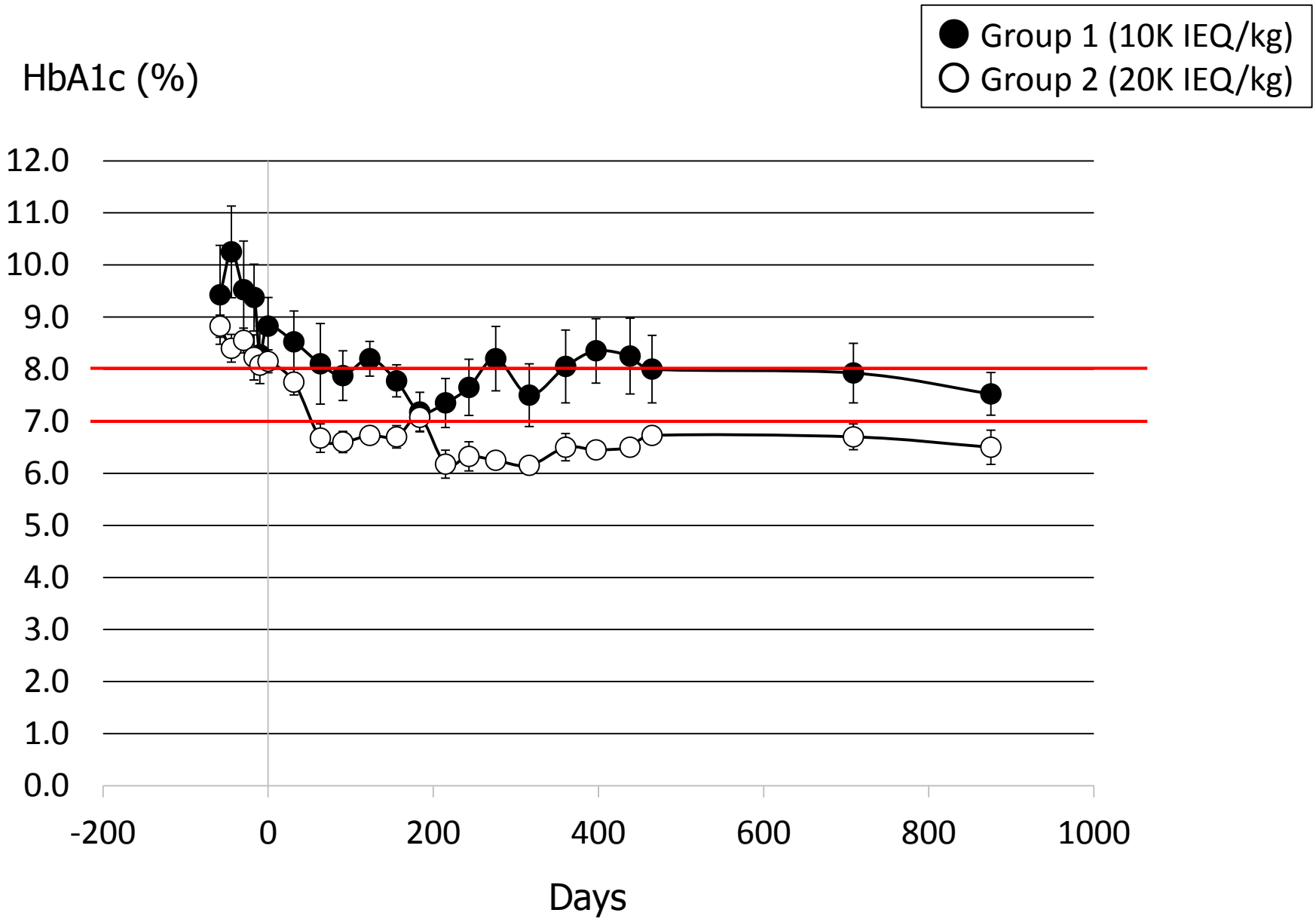
Group	N	Age (y) (mean±SE)	Duration of T1DM (y) (mean±SE)	BMI (kg/m2) (mean±SE)	IEQ/kg (1st) (mean±SE)	IEQ/kg (2nd) (mean±SE)
1	4	30±5	9±2	21±1	5,200±108	5,073±138
2	4	44±7	19±4	27±2	9,034±150	10,064±109

Individual averages of pre- and post-transplant HbA1c, insulin dose and TEF score

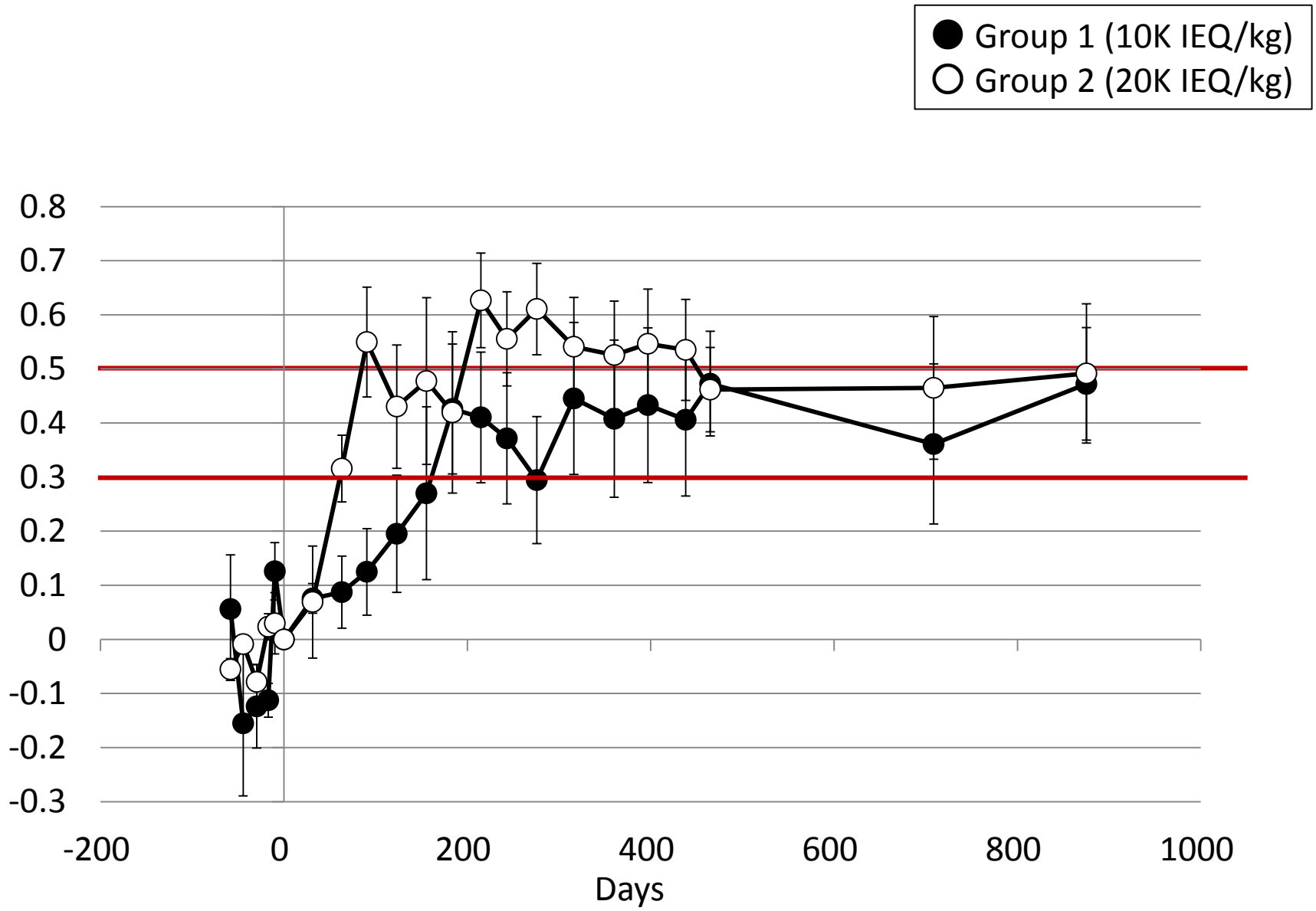


*P<0.05, **P<0.01

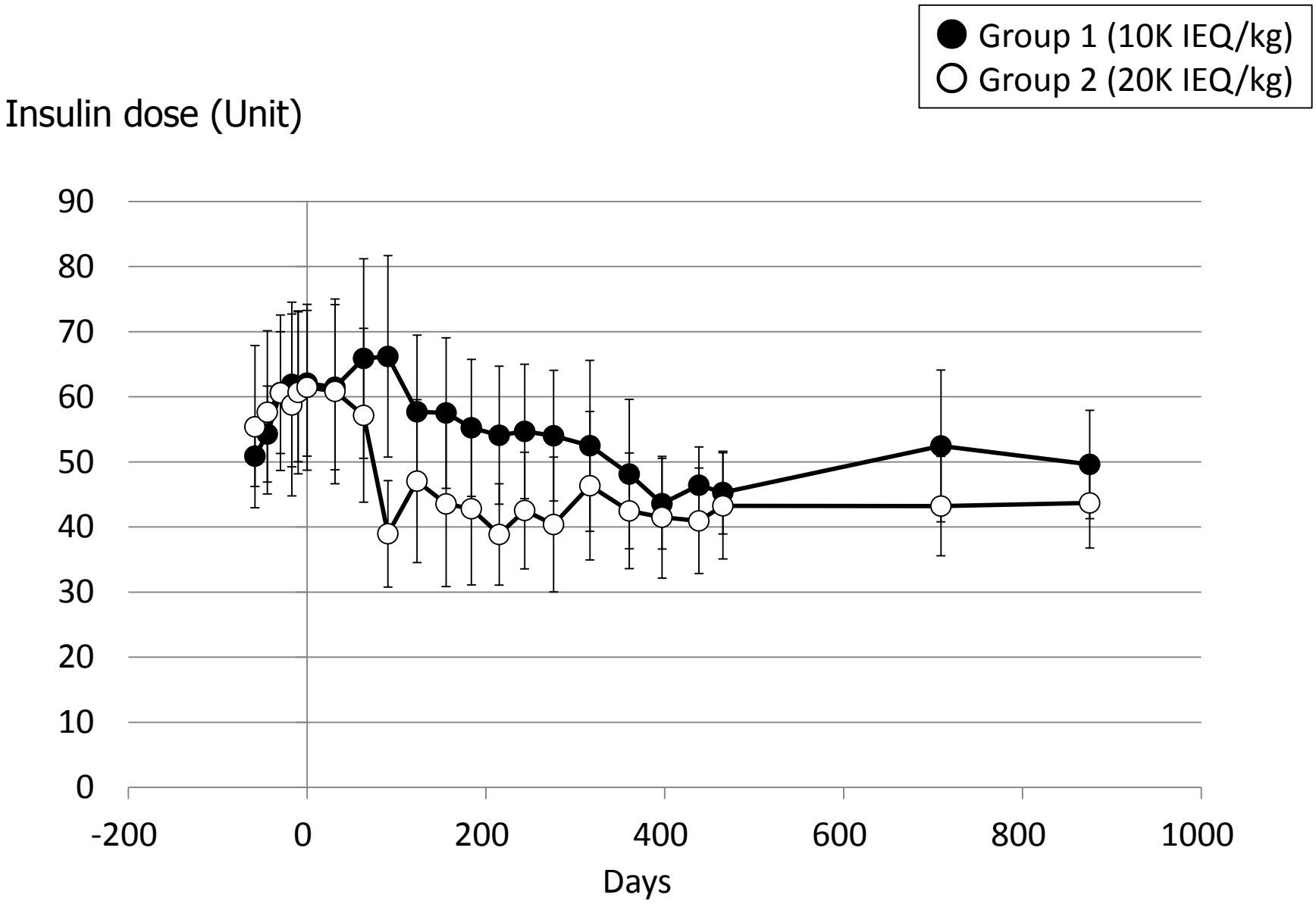
Time course of average HbA1c after Transplantation



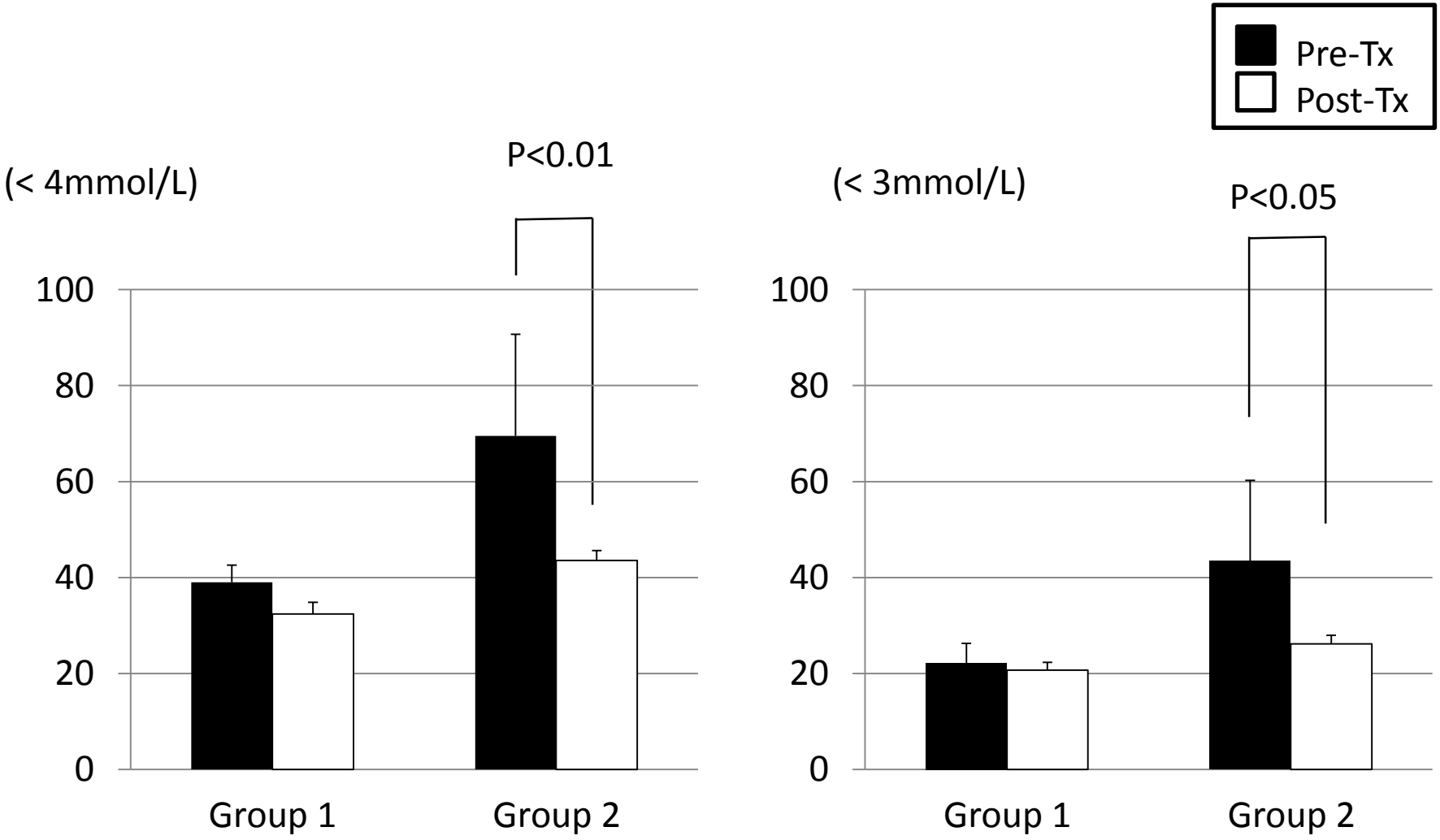
Time course of TEF score after transplantation



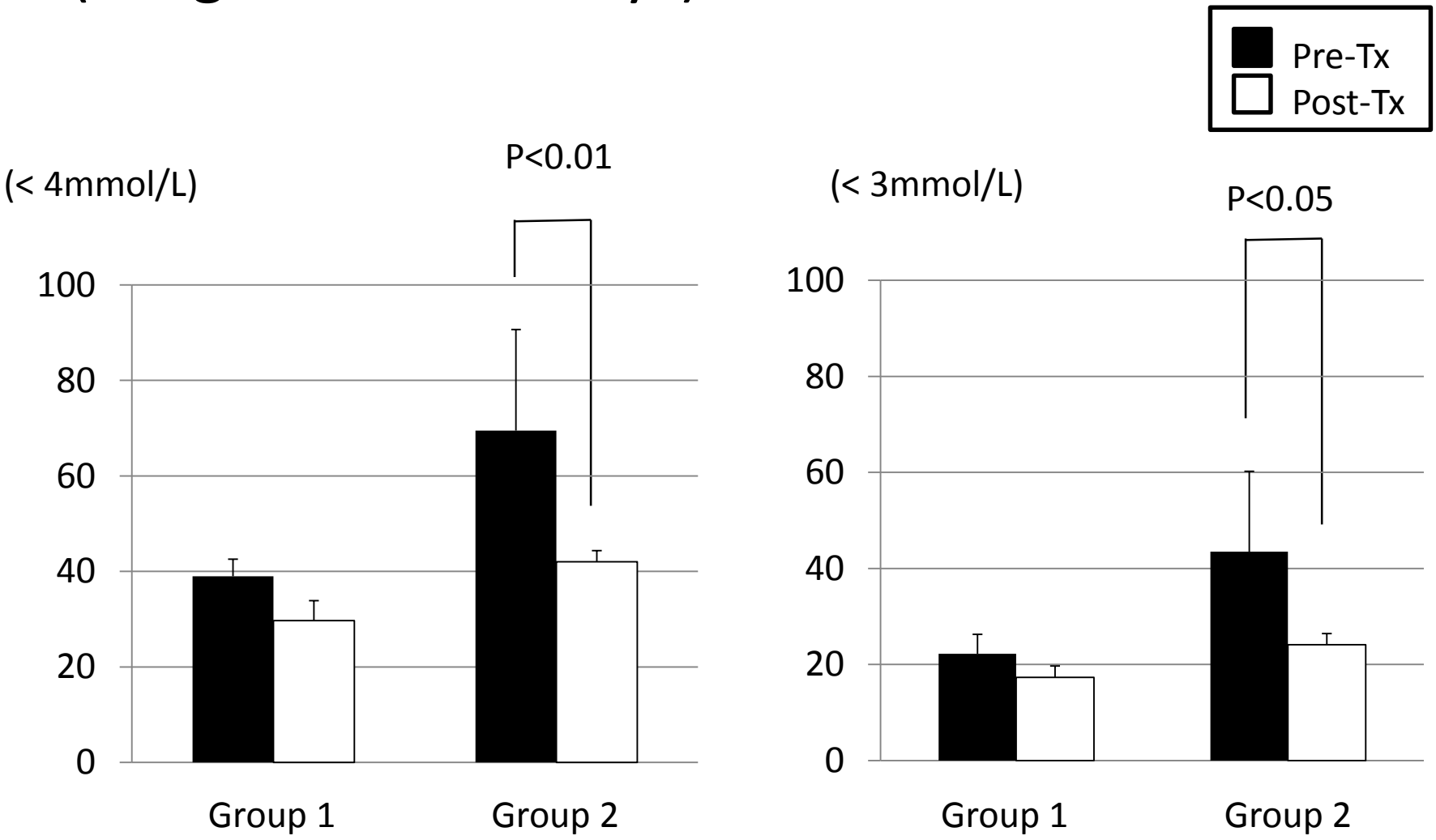
Time course of daily insulin dose after transplantation



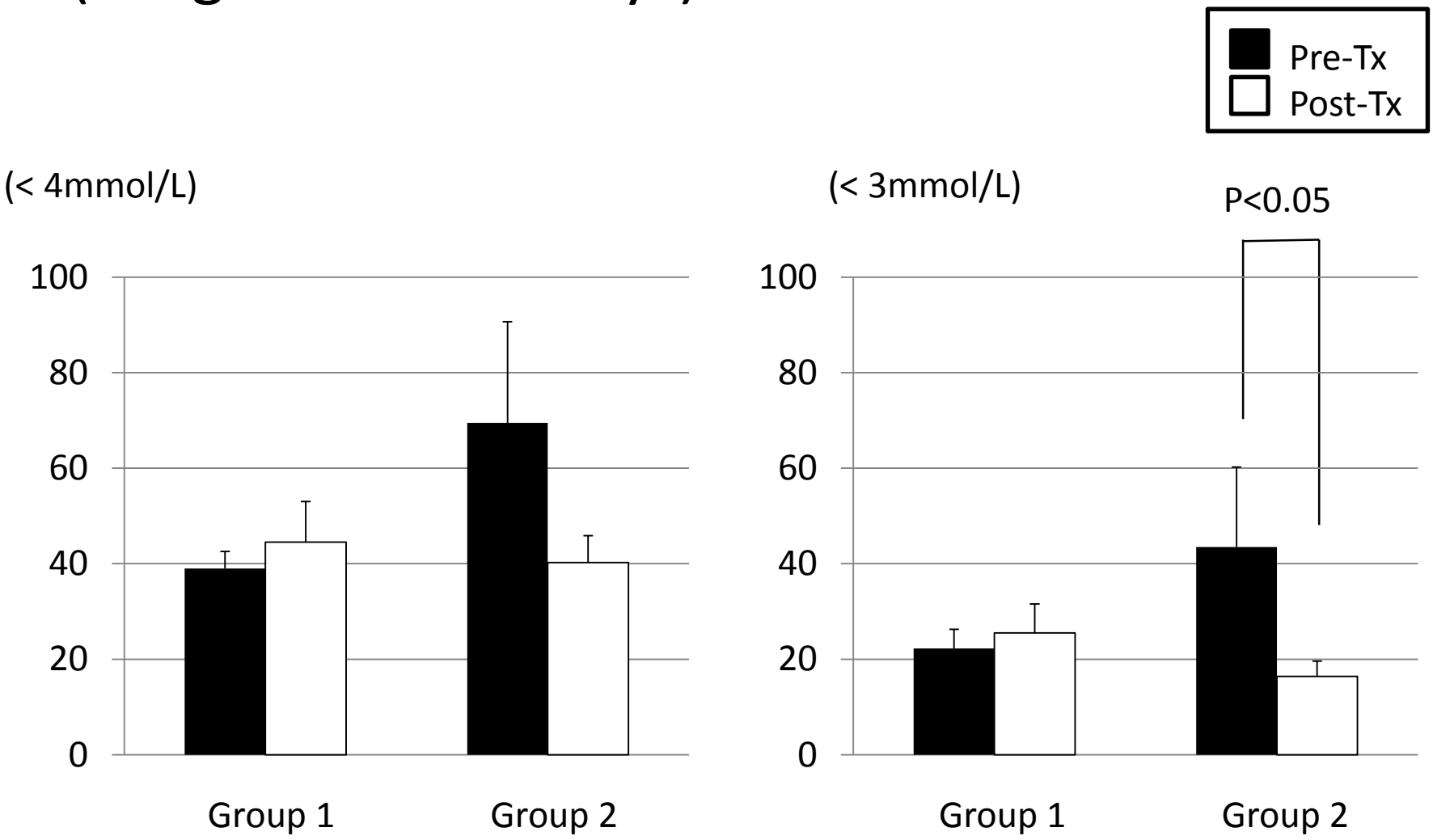
Number of unaware hypoglycemia for 4 weeks



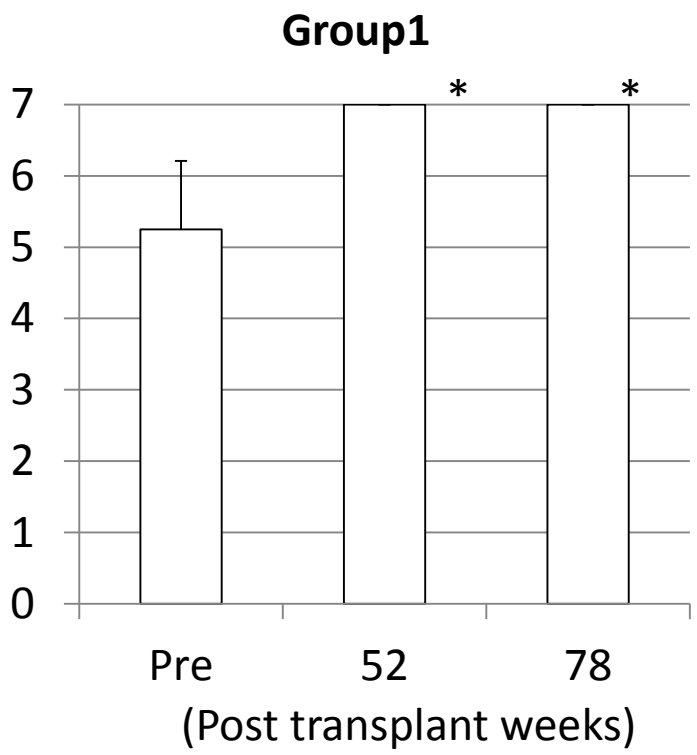
Number of unaware hypoglycemia for 4 weeks (Long-term >300 days)

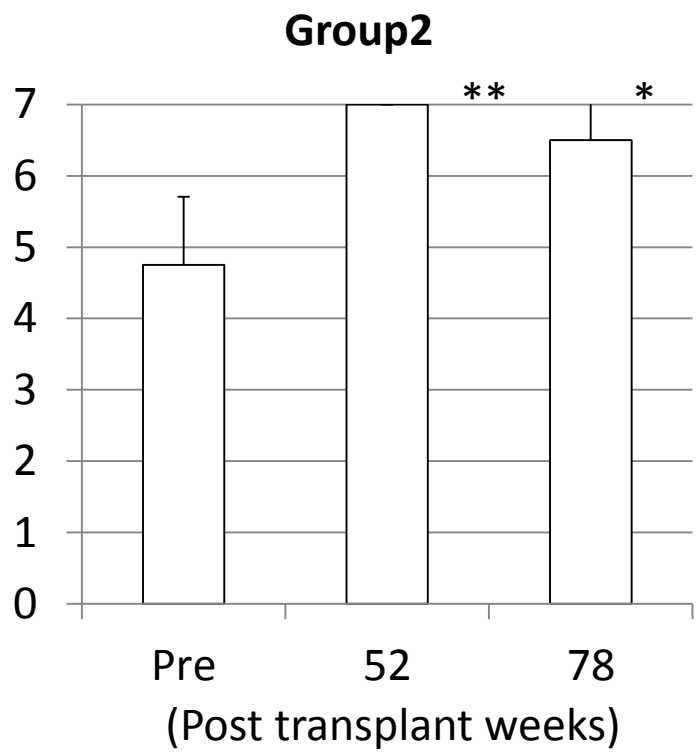


Number of unaware hypoglycemia for 4 weeks (Long-term >600 days)



Patients' treatment satisfaction





(Full satisfaction: 7, No satisfaction:1)

*P<0.05, **P<0.01 compared with Pre-transplantation

Summary

Group 2 (10KIEQ/kg x 2) demonstrated

1. HbA1c less than 7% have been maintained for more than two years with significant reduction of unaware hypoglycemia and no severe hypoglycemia

2. TEF reached the level of insulin independence but actual insulin dose remained high

3. Patients showed high satisfaction with the encapsulated porcine islet transplantation

Future direction of porcine islet xenotransplantation

Target for research

1. Pig source
2. Encapsulation
3. Implant sites
4. Anti-inflammatory drug
5. Anti-rejection drug

Pig Sources

	Fetus, Neonatal	Young	Young adult, Adult	Genetically modified pigs
Age	E-5 days	14-22 days	3M->2 years	Fetus-Adult
Islet isolation	Stable	Stable	Difficult	Depends on age
Immediate function	No	Yes	Yes	Depends on age
Islet yield (IEQ)	8,000-25,000	30,000 (180,000)	80,000-500,000	Depends on age
Clinical experience	Yes	Yes	No	No

Encapsulation

1. Material: Alginate-Ba, Alginate-PLO, Alginate-PLL, Agarose
2. Size: 1.5mm capsule, conformal capsule
3. New Polymers: Ply (2-3)-D-glucopyranoses

Implant sites of encapsulated islet

	Access to blood	Stable distribution	Avoidance of aggregation	Ease of retrieve
Peritoneal cavity	No	No	No	No
Renal subcapsule	Yes	Yes	No	No
Subcutaneous	No	Yes	Yes	Yes
Pre-vascularized subcutaneous	Yes	Yes	Yes	Yes
Omentum pouch	Yes	Yes	Yes	Yes
Portal vein	Yes	Yes	Yes	No

Co-administered drugs

1. Anti-inflammatory for foreign body reaction
2. Immunosuppressant for indirect pathway

Conclusions

1. Encapsulated neonatal porcine islet transplantation can be performed safely

2. Efficacy was improved by high quality of islets but further improvement is needed

3. Pig source, capsules, implant sites, and anti-inflammatory and/or immunosuppressive drugs are next target to improve the efficacy