Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Bioengineering an Intra-Abdominal Endocrine Pancreas

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SUPPLEMENTARY APPENDIX

Clinical History at Onset of Type 1 Diabetes

The patient reported in the letter received a diagnosis of type 1 diabetes at 17 years of age, after she presented with polydipsia, polyuria, polyphagia and an unintended weight loss of approximately 10 lbs over the previous month. She recalled that she had had a glucose level in the 800 mg/dL range at disease onset but could not remember the HbA1c level or confirm a diagnosis of diabetic ketoacidosis. Medical records related to her initial diagnosis are not available, as the patient was living overseas at the time. She was immediately started on insulin therapy.

Pre-transplant Evaluation

At the time of screening evaluation for islet transplantation, insulin requirements obtained from a 28-day glucose-insulin log were 33.30±1.76 units/day. The patient had a Clarke score of 6, consistent with hypoglycemia unawareness.[1] She was experiencing severe hypoglycemia (i.e., requiring assistance) at least once per month during the year before transplantation and had experienced three episodes associated with loss of consciousness requiring glucagon administration.

Pre-transplant evaluation was notable for a fasting C-peptide <0.1 ng/mL (<0.03 nmol/L) and 90-minute C-peptide (following a 2hr mixed meal tolerance test) of 0.15 ng/mL (0.05 nmol/L) with a corresponding glucose of 298 mg/dL (16.39 mmol/L). We assessed the presence of diabetes-associated autoantibodies to glutamic acid decarboxylase (GAD65), insulinoma antigen-2 (IA-2), Zinc transporter protein 8 (ZnT8) and insulin. With the exception of the insulin antibody assay, all autoantibody levels are expressed as an index calculated from the counts per minute of the test sample and the positive and negative control samples. The upper limits of normal were calculated using ROC (Receiver Operating Curves). The patient's results were positive for IA-2 (index 23.3 [normal cut-off 6.4]) and ZnT8 (index 7.9 [normal cut off 3.35]) autoantibodies but negative for GAD65 and insulin autoantibodies. On a 5 month pre-transplant follow-up visit, insulin requirements from 28-day glucose-insulin log were 32.91±1.28 units/day.

Weight Loss after Islet Transplantation

Following islet transplantation, a gradual weight loss of 8.2 Kg was observed by 6 months post-transplant. Her weight stabilized and plateaued at 45.5 Kg after a nutritional evaluation and resumption of a balanced diet. Weight loss post islet transplantation is not unexpected and has been previously reported.[2] Possible contributing factors include optimization of insulin requirements (i.e., elimination of exogenous insulin administration and physiologic endogenous insulin delivery) and a reduction in carbohydrate intake, in part due to the resolution of hypoglycemia.

Homeostatic Model Assessment (HOMA) Indexes

HOMA indexes[3] were calculated to monitor changes in insulin sensitivity and beta cell function longitudinally using the HOMA2 calculator (version 2.2.3 © Diabetes Trials Unit, University of Oxford) available online at http://www.dtu.ox.ac.uk/homacalculator.

HOMA2-IR (insulin resistance) declined over time. HOMA2-%B (β-cell function) improved by 6 months in line with metabolic responses observed during MMTT. A decline in HOMA2-%B was observed at 12 months, which was accompanied by a progressive increase in HOMA-2%S (insulin sensitivity).

BETA Scores

The validated β-score[4] and BETA-2 score[5] were utilized as composite measures of beta cell function following islet transplantation.

At 6 months, she had a β-score of 8, which indicated overall excellent graft function, while the BETA-2 score of 15, associated with insulin independence, provided further information regarding glycemic control as this value is also associated with glucose intolerance and the patient had a 90-minute glucose of 165 mg/dL (Fig., Panel C).

At 12 months, the β-score decreased to 7, a value still associated with insulin independence and overall good graft function. Notably, the BETA-2 score markedly decreased to 10, a value generally associated with loss of insulin independence. Although the patient had decreased insulin secretory responses to a mixed meal tolerance test, her overall glycemic control evaluated by 7-day continuous glucose monitoring was 109±15 mg/dL (range 73-151 mg/dL, n=1876) not necessitating reintroduction of insulin therapy. The patient has continued to exercise regularly doing mostly aerobic exercises and follows a healthy low carbohydrate diet. We speculate that these factors likely contribute to her stable glycemic control.

REFERENCES

1. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995;18:517-22.
2. Poggioli R, Enfield G, Messinger S, et al. Nutritional status and behavior in subjects with type 1 diabetes, before and after islet transplantation. Transplantation 2008;85:501-6.
3. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-95.
4. Ryan EA, Paty BW, Senior PA, Lakey JR, Bigam D, Shapiro AM. Beta-score: an assessment of beta-cell function after islet transplantation. Diabetes Care 2005;28:343-7.
5. Forbes S, Oram RA, Smith A, et al. Validation of the BETA-2 Score: An Improved Tool to Estimate Beta Cell Function After Clinical Islet Transplantation Using a Single Fasting Blood Sample. Am J Transplant 2016;16:2704-13.