Restoration of Hypoglycemia Awareness after Islet Transplantation

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**Objective:** To determine the impact of islet transplantation (ITx) on hypoglycemia awareness in patients with unstable type 1 diabetes mellitus (T1DM) and its relation to islet function.

**Research design and methods:** Thirty-one ITx recipients were studied. Hypoglycemia unawareness was assessed utilizing the *Clarke hypoglycemic-score* (0=no hypoglycemia; ≥4=hypoglycemia unawareness). Subjects were grouped based on graft function: off-insulin (n=8), graft dysfunction (GDF; on-insulin and stimulated C-peptide≥0.3 ng/ml, n=13) and graft failure (GF; stimulated C-peptide<0.3 ng/ml, n=10, evaluated 11.5±14.5 months after GF).

**Results:** The hypoglycemia score improved following ITx when compared to baseline values (pre vs. post: 5.29±1.51 vs. 1.35±1.92, P<0.001). This result was sustained even after patient stratification based on islet function (pre vs. post off-insulin: 5.63±2.00 vs. no hypoglycemia reported; GDF: 5.31±1.49 vs. 1.15±1.63, P<0.001 and GF: 5.00±1.16 vs. 2.70±2.26, P=0.014).

**Conclusions:** The improved metabolic control achieved with ITx can restore hypoglycemia awareness in patients with T1DM, persisting even after islet GF.
Occurrence of hypoglycemia is the major limitation of intensive control aimed at A1C normalization in patients with type 1 diabetes mellitus (T1DM). Frequent hypoglycemic episodes are particularly common in subjects with unstable T1DM and can lead to hypoglycemia unawareness. Although islet transplantation (ITx) prevents severe hypoglycemia (1) and restores some counter-regulatory hormone secretion (2), data showing its effects on restitution of hypoglycemia awareness are not conclusive (2,3).

The aim of this study was to determine if the optimal metabolic control achieved by ITx can restore hypoglycemia awareness and whether or not these effects persist after islet graft failure (GF).

RESEARCH DESIGN AND METHODS
A retrospective cohort study was conducted on 31 T1DM recipients of ITx (ITx alone n=25; islet after kidney n=6) between 2001 and 2007. Procedures were performed as described (1) under protocols approved by the University of Miami health research ethics board and informed consent was obtained from each subject.

Hypoglycemia unawareness was assessed, utilizing the Clarke hypoglycemic-score (minimum=0; maximum=7; no hypoglycemia=0; hypoglycemia unawareness≥4) (4) twice, including pre-ITx and at the most recent follow-up (47.2±21.3 months after first ITx). Subjects were grouped based on graft function: off-insulin (n=8), graft dysfunction (GDF; restarted insulin and stimulated C-peptide≥0.3 ng/ml, n=13) and GF (stimulated C-peptide<0.3 ng/ml; n=10, evaluated 11.5±14.5 months after GF).

Plasma glucose (hexokinase method) and C-peptide (double antibody radioimmunoassay) were measured during a mixed meal test. A1C [HPLC, BioRad, Richmond, CA, normal values: 4.2-6.1%] was determined before ITx and at the most recent follow-up.

Proportions were compared by with the chi²-test. The paired t-test was used to compare variables pre- and post-ITx, and one-way ANOVA was used to compare the post-ITx hypoglycemic-score among groups. P values (2-tailed) <0.05 and <0.016 (Bonferroni correction for differences among subgroups) were considered significant.

RESULTS
Patients age at baseline was 43.8±8.7 years, and diabetes duration was 29.3±11.8 years. Subjects were white and 13 (42%) were males. Thirteen subjects (42%) had hypertension and 11 (35%) had dyslipidemia. Diabetes complications at baseline included retinopathy (71%; n=22; 14 proliferative), neuropathy (45%; n=14; 4 autonomic, 7 peripheral and 3 both) and nephropathy (29%; n=9; 3 microalbuminuria and 6 with a kidney transplant 9.1±6.3 years old).

Mean hypoglycemic-score pre-ITx was 5.29±1.51 and was inversely correlated with pre-ITx glycemic control as measured by A1c (r=-0.370, P=0.040). A decrease in hypoglycemic-score was observed post-ITx (1.35±1.92, P<0.001). Similarly, there was a reduction in the proportion of patients with hypoglycemia unawareness (pre vs. post: 87 vs. 13%, P<0.001) and an increase in glycemic threshold that resulted in symptoms (pre vs. post: 41.4±17.6 vs. 58.4±10.3 mg/dl, P=0.001). Results were sustained even after patient’s stratification based on islet function (pre vs. post off-insulin: 5.63±2.00 vs. no hypoglycemia reported; GDF: 5.31±1.49 vs. 1.15±1.63, P<0.001 and GF: 5.00±1.16 vs. 2.70±2.26, P=0.014) (Figure 1); however, an increase in post-ITx hypoglycemic-score was
observed as patients lost graft function (P=0.007).

A1C improved in off-insulin (6.8±0.8 vs. 6.0±0.6, P=0.038) and GDF (7.5±1.2 vs. 6.7±0.5, P=0.022) subjects, and no further deterioration was observed after GF (7.0±0.9 vs. 7.4±0.9, P=0.318), suggesting that recovery of awareness was a consequence of glycemic stability rather than metabolic deterioration associated with a less strict therapy.

Additionally, a lower hypoglycemia score correlated with better beta-cell function (r=-0.440, P=0.013 and r=-0.496, P<0.001, post-ITx fasting and stimulated C-peptide, respectively). Follow-up was similar for all groups (49.3±20.3 vs. 42.7±22.2 vs. 51.5±21.9 months, P=0.602) and no clinical or laboratory factors were associated with hypoglycemia unawareness post-ITx, including diabetes duration and presence of neuropathy (data not shown).

CONCLUSIONS

In this sample of unstable T1DM patients, glucose stabilization after ITx was associated with restoration of hypoglycemia awareness. Interestingly, improvements in hypoglycemia awareness were sustained even after GF.

Restoration of hypoglycemia awareness can be achieved with medical treatment or pancreatic transplantation. Medical treatment is driven by hypoglycemia avoidance but can lead to metabolic deterioration if it is necessary to lower the insulin dose (5). Pancreatic transplantation reestablishes normal glucose homeostasis (6), but the surgical risks are a limitation.

No hypoglycemia has been reported after ITx in patients achieving insulin independence (1). After developing GDF and reintroducing exogenous insulin, hypoglycemic episodes may resume, though with a much lower frequency than pre-ITx. Based on these observations, it is conceivable that ITx recipients regain adrenergic symptoms. Indeed, an improvement in hypoglycemia awareness following ITx was suggested by a small sample short-term clamp study (2), although the literature is not consistent (3).

To the best of our knowledge, this is the first report of restoration of hypoglycemia awareness after ITx, which includes more than a few patients and with a longer follow-up, and we have demonstrated statistically significant benefits even after GF. No hypoglycemia was reported by off-insulin subjects; the recovery of hypoglycemia awareness found in patients with GDF was predictable and was probably related to tight glycemic control due to ITx and prevention of hypoglycemia. In GF patients, avoidance of hypoglycemia during the early post-ITx period possibly led to increased awareness, which was maintained after loss of graft function. Hypoglycemia unawareness relapse was observed in this group, even though the score remained in the normal range.

The retrospective design of this study did not allow for more frequent evaluations and better description of patient symptoms that would have enhanced the study. Despite this limitation the restoration of hypoglycemia awareness.

In conclusion, the stable metabolic control achieved by ITx restores hypoglycemia awareness in T1DM subjects. These benefits were accomplished without metabolic deterioration, independent of diabetes duration or presence of autonomic neuropathy, and persisted beyond the duration of islet graft function.

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REFERENCES
Legend:

Figure 1. (A) Hypoglycemic-score [Clarke score; reference 4] and (B) proportion of subjects with hypoglycemia unawareness (hypoglycemic-score ≥4) pre and post islet transplantation, according to islet function. P=0.007 for comparison of post-transplant hypoglycemic-score between off-insulin and graft failure groups. *P value is not applicable as no hypoglycemia was reported post-transplant.