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CLINICAL RESEARCH SHORT REPORT

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Long-term effects of pancreatic islet transplantation on polyneuropathy in patients with brittle diabetes: A single-center experience

Mohammed Alhaidar MD[1] | Betty Soliven MD[1] | Chuanhong Liao MS[2] | Helene Rubeiz MD[1] | Mateusz Ogledzinski MD[3] | Piotr Witkowski MD[3] | Kourosh Rezania MD[1]

[1]Department of Neurology, Biological Science Division, University of Chicago, Chicago, Illinois, USA

[2]Department of Public Health Sciences, Biological Science Division, University of Chicago, Chicago, Illinois, USA

[3]Department of Surgery, Biological Science Division, University of Chicago, Chicago, Illinois, USA

Correspondence
Kourosh Rezania, Department of Neurology, University of Chicago, 5841 S. Maryland Ave, MC 2030, Chicago, IL 60637, USA.
Email: krezania@bsd.uchicago.edu

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Abstract

Introduction/Aims: Pancreatic islet transplantation (ITx) is increasingly used in patients with brittle type 1 diabetes (T1D). If successful, ITx results in insulin-free euglycemia, but its application is limited by a need for lifelong immunosuppression. The aim of this study was to assess the long-term effects of ITx on the occurrence and course of polyneuropathy in a cohort of patients with brittle T1D.

Methods: In this prospective, single-center study, 13 patients (4 males and 9 females) with brittle T1D had a baseline neurological exam with the calculation of Utah Neuropathy Scale (UNS) and a limited nerve conduction study before ITx, and about yearly after in the patients who achieved insulin independence.

Results: Patients were followed for a period of 17 to 133 months. There was no significant difference between UNS and nerve conduction study parameters at baseline and at the end of follow-up, except for significant decreases in peroneal (50.34 ± 6.12 vs. 52.42 ± 6.47 ms, $P = 0.005$) and ulnar (27.5 ± 2.15 vs. 29.45 ± 2.10 ms, $P = 0.009$) F-wave latencies and an increase in ulnar sensory nerve conduction velocity (49.98 ± 6.27 vs. 47.19 ± 5.36 m/s, $P = 0.04$).

Discussion: If successful, ITx has a good long-term safety profile for peripheral nerve toxicity, and a favorable effect on diabetic neuropathy.

KEYWORDS
brittle diabetes, F wave, islet transplantation, neuropathy

1 | INTRODUCTION

Brittle type 1 diabetes (T1D) is defined by unpredictable variability in blood glucose levels, episodic severe hypoglycemia with unawareness, and periods of ketoacidosis.[1] Pancreatic islet transplantation (ITx) is a promising treatment for brittle T1D through restoring glucose-

Abbreviations: ITx, islet transplantation; T1D, type 1 diabetes; NCV, nerve conduction velocity; UNS, Utah Neuropathy Scale.

regulated endogenous insulin secretion.[2,3] ITx has also been performed for patients with brittle T1D who have diabetic complications, those who receive immunosuppression for kidney and/or liver transplantation, as well as in patients with chronic pancreatitis who have intractable pain and are undergoing total pancreatectomy.[4,5] As euglycemia is attained in most patients who undergo a successful ITx, the procedure has a favorable effect (prevention, stabilization, or partial improvement) on diabetic microvascular complications, including polyneuropathy.[6] In this study we investigated the long-term effects of ITx on the occurrence and course of polyneuropathy in a cohort of patients with brittle T1D.

2 | METHODS

The study was approved by the institutional review board of the University of Chicago Biological Science Division. The subject selection and general methodology of the study have been described elsewhere.[7] The neurological evaluation was based on: (1) clinical evidence for neuropathy and its severity, using the Utah Neuropathy Scale (UNS)[8]; and (2) limited nerve conduction study that consisted of bilateral sural (recorded behind the lateral malleolus), right superficial radial (recorded from snuffbox) and right ulnar (recorded from digit V) sensory responses, right peroneal (recorded from extensor digitorum brevis) and ulnar (recorded from abductor digiti minimi) motor responses, as well as right peroneal and right ulnar minimal F-wave latencies. Neurological examinations and electrodiagnostic evaluations were done by one of the authors (K.R., B.S., H.R.), using three different electromyography machines (Natus, Middleton, WI, USA) over the study duration. Neurological evaluation and electrodiagnostic testing were done before first ITx and about yearly afterward in the patients with a successful ITx.

2.1 | Statistical analysis

Data were analyzed before the ITx and at the last follow-up visit. Continuous data were tested by Shapiro–Wilk test to assess for normal distribution. Data with a normal distribution are presented as mean ± standard deviation and were analyzed by a paired *t* test. Other data are presented as median and range, and were analyzed using the Wilcoxon signed-rank test for significance. $P < 0.05$ was considered statistically significant.

3 | RESULTS

Thirteen patients (4 males and 9 females) with type 1 brittle diabetes mellitus were enrolled in this study from 2004 to 2014 and followed for a period of 75.5 ± 36.7 months after receiving the first ITx. Three of 13 patients had two and 7 of 13 had three transplantations (Table 1). An insulin-free posttransplant glycosylated hemoglobin level of less than 7% was achieved and sustained in 11 of 13 patients. Two patients underwent pancreas transplantation after the third ITx, because of loss of response, one shortly before and the other after the last follow-up visit. All patients underwent clinical and neurophysiological assessments at baseline and at the follow-up visits. At the visit before the transplantation, 5 of 13 patients had a UNS of 0. The rest had symptomatology of a distal polyneuropathy (UNS of 2 to 16). There was no difference in the UNS at baseline versus follow-up (Table 2). None of five patients without baseline neuropathy symptoms developed

TABLE 1 Demographics, number of ITxs, follow-up, and immunosuppression regimens

Patient	Age[a] (years)/sex	#ITx	Follow-up (months)	Immunosuppression
1	40 female	3	133	D, Rap, T
2	33 male	3	100	D, Rap, T
3	47 female	3	60	D, Rap, T
4	49 female	3	111	D, Rap, T
5[b]	45 male	3	96	Thy, T, M
6	50 female	3	62	Thy, T, M, Rep
7[b]	36 female	3	66	Thy, T, M
8	52 male	1	104	Thy, T, M, Rep
9	55 male	1	112	Thy, T, M, Rep
10	48 female	2	29	Thy, T, M
11	38 female	1	17	Thy, T, M, Rep
12	30 female	2	63	Thy, T, M
13	56 female	2	29	Thy, T, M, Rep

Abbreviations: D, daclizimab, #ITx, number of islet transplantations; M, mycophenolate mofetil; Rap, rapamycin, Rep, reparixin, T, tacrolimus; Thy, thymoglobulin induction.
[a]Age at the time of first transplantation.
[b]Received a pancreatic transplant after failure of third ITx.

TABLE 2 Comparison of age, glycosylated hemoglobin, neuropathy score, and neurophysiological parameters before ITx and at last follow-up

Parameter	Before ITx	Last follow-up	*P* value
Age (years)	44.54 ± 8.39	51.00 ± 8.81	-
Glycosylated hemoglobin (%)	7.55 ± 0.85	5.91 ± 1.01	0.003
Utah Neuropathy Scale score	2 (0–16)	2 (0–18)	0.54
Average sural amplitude (μV)	10.5 (0–45.5)	8.3 (0–41.7)	0.38
Average sural conduction velocity (m/s)	44.29 ± 4.54	45.00 ± 5.84	0.37
Peroneal amplitude (mV)	6.22 ± 4.29	5.05 ± 4.12	0.08
Peroneal conduction velocity (m/s)	39.45 (37.4–57.3)	41.6 (29.1–53.5)	0.09
Peroneal F-wave latency (ms)	52.42 ± 6.47	50.34 ± 6.49	0.005
Ulnar motor amplitude (mV)	13.95 ± 6.05	14.46 ± 5.20	0.62
Ulnar motor conduction velocity (forearm) (m/s)	52.83 ± 5.50	55.36 ± 7.19	0.15
Ulnar motor conduction velocity (elbow) (m/s)	54.73 ± 10.07	54.31 ± 9.78	0.86
Ulnar F-wave latency (ms)	29.45 ± 2.10	27.5 ± 2.15	0.009
Ulnar sensory amplitude (μV)	25.29 ± 23.13	25.30 ± 21.32	0.6
Ulnar sensory velocity (m/s)	47.19 ± 5.36	49.98 ± 6.27	0.04
Radial sensory amplitude (μV)	29.78 ± 19.29	25.16 ± 14.45	0.14
Radial sensory velocity (m/s)	53.97 ± 4.89	55.0 ± 7.18	0.3

Abbreviation: μV, microvolt; ms, millisecond; m/s, meters per second; mV, millivolt.
Note: Data expressed as mean ± standard deviation or median (range).

them at the end of the follow up period. In the patients who had a UNS of over 0, there was slight deterioration (increase of 2 to 5 points) in three, slight improvement (decrease of 2 points) in two, and no change in the other three (Figure S1 and Table S1). The mean of peroneal and ulnar F-wave latencies decreased significantly and the ulnar sensory velocity increased at the last follow-up visit. There were no other significant changes in the conduction study parameters (Table 2 and Figure S1).

4 | DISCUSSION

Our study findings confirm and extend the accumulating data that a successful ITx has a favorable effect on long-term outcome in terms of stabilization of diabetic neuropathy. The latter can be attributed to attaining euglycemia after a successful ITx. It is well established that aggressive control of blood sugar decreases the long-term burden of diabetic microvascular complications, including neuropathy. For example, in the Diabetes Control and Complications Trial, 6.8% and 5.6% of patients in the intensive and conventional arms had neuropathy at baseline, which increased to 9.3% and 17.5%, respectively, after a mean follow-up of 6.5 years.[9] Successful pancreatic transplantation results in further improvement in clinical score and neurophysiological parameters of neuropathy,[10,11] but the invasive nature of the procedure has resulted in development of the much less invasive ITx. The favorable effects of ITx on hyperglycemia and hypoglycemic episodes are countered by the lifelong need for steroid-free immunosuppression. All participants in this study were on therapeutic doses of tacrolimus, which has the potential to cause neurotoxicity, including polyneuropathy.[12,13] We found that ITx and the accompanying immunosuppressive regimen exhibited a good safety profile from the standpoint of potential peripheral nerve toxicity. Other side effects of the procedure and immunosuppressants have been reported previously.[7]

Overall, the results of this study are in line with previous longitudinal studies on ITx but over a longer follow-up period. Ryan et al. found that 32% of patients who underwent ITx had a neuropathy at baseline, and there was no difference in neuropathy severity after 5 years according to neurothesiometer score.[14] Thompson et al. showed there was a trend for improvement of average nerve conduction velocity (NCV) of seven nerves in those patients who received ITx when compared with a medically treated group, over a period of 66 months.[15] Del Carro et al. assessed the progression of neuropathy in 18 patients with T1D and end-stage renal disease after they underwent successful ITx after kidney transplant and compared them with a control group with kidney transplant alone.[16] The nerve conduction study parameters included a NCV index and amplitudes of compound muscle action potentials and sensory nerve action potentials, which improved over a period of 4 years and then stabilized in the patients with kidney transplant + ITx but did not change in the kidney-transplant-alone group.

In this study we have undertaken a long-term investigation of peripheral nerve function for ITx, with some patients followed for more than a decade. Besides the longitudinal nerve conduction studies, we also assessed the UNS, a sensitive tool to detect a distal sensory (including a small-fiber) neuropathy.[8] The minimum F-wave latency of the ulnar and peroneal nerves decreased significantly in the follow-up evaluation. This finding suggests a favorable effect of ITx on neuropathy, as the minimal F-wave latency was the most sensitive nerve conduction study parameter for detecting early diabetic neuropathy in several earlier studies.[17–19] Furthermore, F-wave latency was the only nerve conduction study parameter

that improved after treatment with epalrestat, an aldose reductase inhibitor[20] that is now commercially available for the treatment of diabetic neuropathy in Japan. Mild improvement of F-wave latencies likely does not translate into a clinical change.

The limitations of this study include: (1) its small sample size, which precludes drawing any conclusions about potential rare neurological adverse effects of the procedure or associated immunosuppressive treatments and, furthermore, this study did not have enough power to detect a small clinical improvement in UNS; and (2) lack of neurological follow-up on patients in whom the ITx failed.

5 | CONCLUSION

In this single-center, prospective study, patients who underwent a successful ITx did not develop significant peripheral nerve toxicity. UNS and nerve conduction study parameters remained stable or improved in most, but not all, of the patients.

AUTHOR CONTRIBUTIONS

Mohammed Alhaidar: Writing – original draft; methodology; formal analysis; project administration; data curation. **Betty Soliven:** Writing – original draft; formal analysis; project administration. **Chuanhong Liao:** Formal analysis; supervision; writing – original draft. **Helene Rubeiz:** Writing – original draft; project administration. **Mateusz Ogledzinski:** Writing – original draft; project administration. **Piotr Witkowski:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; project administration; resources. **Kourosh Rezania:** Conceptualization; investigation; writing – original draft; methodology; formal analysis; project administration; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

P.W. was a paid consultant to Dompe Farmaceutici S.p.A. for another study involving liver transplantation. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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