Corneal Confocal Microscopy Shows an Improvement in Small-Fiber Neuropathy in Subjects With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion Compared With Multiple Daily Injection

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Improved glycemic control is the only treatment that has been shown to be effective for diabetic peripheral neuropathy in patients with type 1 diabetes (1). Continuous subcutaneous insulin infusion (CSII) is superior to multiple daily insulin injection (MDI) for reducing HbA_{1c} and hypoglycemic events (2). Here, we have compared the benefits of CSII compared with MDI for neuropathy over 24 months.

A total of 49 subjects with T1DM (18 on CSII vs. 31 on MDI) and 40 age-matched control subjects underwent assessment of vibration perception threshold (VPT), cold threshold (CT), warm threshold (WT), neurophysiology, deep breathing heart rate variability (DB-HRV), intraepidermal nerve fiber density (IENFD), and corneal nerve fiber density (CNFD), branch density (CNBD), and fiber length (CNFL) at baseline and after 24 months.

At baseline, subjects on CSII and MDI were matched for duration of diabetes, HbA_{1c}, blood pressure, total cholesterol, HDL, and triglycerides, which did not change over 24 months (Table 1). Both CSII and MDI groups showed comparable evidence of large- and small-fiber neuropathy compared with control subjects. Over 24 months there was no change in VPT, CT, WT, neurophysiology, or IENFD in either cohort, but there was a significant increase in CNFD ($P = 0.05$), CNBD ($P = 0.006$), and CNFL ($P = 0.003$), with a significant decrease in DB-HRV ($P = 0.03$) in the CSII group (Table 1).

Previous studies have demonstrated that initiation of CSII can achieve near-normal glycemia and an improvement in nerve conduction as well as painful neuropathy (3). In the current study, the MDI group showed no significant change, but the CSII group showed an improvement in corneal nerve morphology, consistent with regeneration. The improvement in corneal nerve morphology with no change in any other measure of neuropathy echoes our recent findings in patients after simultaneous pancreas kidney transplantation (4). Other markers of small-fiber neuropathy, including quantitative sensory testing and the gold standard IENFD, showed no change, suggesting that corneal confocal microscopy may be more sensitive in detecting small nerve fiber repair.

The current study showed no change in nerve conduction studies in either group, but this may not be unexpected given that glycemic control did not change, and nerve conduction velocity may reflect a more acute effect of improved glucose control. We have no explanation for the paradoxical worsening of autonomic function.

Compared with previous studies assessing the effects of CSII on neuropathy, the main difference in the current study is that the subjects were already on CSII at baseline and we did not actively undertake any change in intervention. Despite suboptimal and comparable glycemic control in both CSII and MDI groups, small-fiber regeneration was evident only in the CSII group, which therefore cannot be attributed to improved glycemic control. We can only speculate that CSII may provide more stable blood glucose control, or alternatively there may be a direct neurotrophic role of insulin on nerves and hence neuropathy (5).

We conclude that CSII may promote small-fiber regeneration, which can be readily detected using corneal confocal microscopy, providing further support for this technique as a surrogate end point of human diabetic neuropathy.

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Table 1—Demographic and clinical parameters and neuropathy assessments in control and type 1 diabetic subjects at baseline and 24 months

	Control		MDI		CSII	
	Baseline	24 months	Baseline	24 months	Baseline	24 months
Age (years)	53.2 ± 2.2	—	55.4 ± 2.9	—	49.9 ± 3.3	—
BMI (kg/m^2)	26.4 ± 0.7	26.2 ± 1.1	27.4 ± 0.9	27.3 ± 0.7	26.0 ± 0.9	27.3 ± 1.4
Duration of diabetes (years)	—	—	34.8 ± 3.1	—	35.2 ± 3.6	—
Blood pressure (mmHg)	129.7 ± 2.6/ 72.7 ± 1.6	116.9 ± 5.8/ 65.5 ± 3.1	136.5 ± 5.59/ 74.7 ± 2.3	127.9 ± 4.0/ 66.3 ± 1.7	138.5 ± 4.1/ 71.7 ± 1.2	135.8 ± 6.3/ 68.6 ± 2.9
HbA_{1c}						
%	5.5 ± 0.1	5.2 ± 0.4	8.3 ± 0.3#	8.2 ± 0.8	8.1 ± 0.2#	8.0 ± 0.2
mmol/mol	37.1 ± 0.5	33.7 ± 0.7	66.7 ± 2.8#	66.2 ± 3.9	64.2 ± 2.7#	63.9 ± 2.3
eGFR (mL/min/1.73 m^2)	84.3 ± 1.1	83.2 ± 1.8	79.8 ± 3.2	72.2 ± 3.9	84.8 ± 3.3	77.2 ± 3.9
Cholesterol (mmol/L)	5.1 ± 0.2	4.6 ± 0.2	4.1 ± 0.1#	4.2 ± 0.2	4.6 ± 0.3#	4.3 ± 0.3
HDL (mmol/L)	1.6 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.7 ± 1.3	1.4 ± 0.1
LDL (mmol/L)	2.7 ± 0.1	2.4 ± 0.2	1.8 ± 0.1#	1.9 ± 0.1	2.5 ± 0.2#	2.2 ± 0.3
Triglycerides (mmol/L)	1.5 ± 0.1	1.3 ± 0.2	1.2 ± 0.2	1.0 ± 0.1	0.9 ± 0.2	1.1 ± 0.1
NSP	0.1 ± 0.1	0.1 ± 0.1	4.8 ± 1.4*	5.0 ± 1.4	2.4 ± 1.2*	2.9 ± 1.2
NDS	0.6 ± 0.3	0.3 ± 0.2	3.7 ± 1.7#	3.7 ± 0.7	3.9 ± 0.9#	3.2 ± 0.9
VPT (V)	6.2 ± 1.3	6.3 ± 1.3	15.9 ± 2.5*	16.9 ± 2.2	14.6 ± 2.9*	15.2 ± 3.1
PMNCV (m/s)	48.7 ± 1.2	49.1 ± 1.2	40.5 ± 1.1*	40.7 ± 1.1	38.8 ± 2.2*	38.4 ± 2.1
PMNA (mV)	6.3 ± 0.5	6.1 ± 0.5	3.1 ± 0.5*	3.2 ± 0.2	2.7 ± 0.6*	2.5 ± 0.5
SNCV (m/s)	50.5 ± 0.8	50.1 ± 0.8	40.7 ± 1.4*	38.9 ± 1.3	43.3 ± 2.0*	40.4 ± 2.4
SNAP (μV)	18.3 ± 1.3	22.8 ± 1.9	7.4 ± 1.1*	7.2 ± 1.1	10.0 ± 2.3*	8.3 ± 2.0
DB-HRV	30.6 ± 2.3	27.1 ± 2.2	25.1 ± 3.7	20.0 ± 3.1	28.9 ± 4.5	22.5 ± 2.7~
CT (°C)	28.4 ± 0.3	28.1 ± 0.4	25.5 ± 0.9#	23.4 ± 1.4	22.9 ± 2.3#	22.0 ± 1.0
WT (°C)	37.1 ± 0.4	37.9 ± 0.8	39.5 ± 0.8#	41.3 ± 0.8	40.2 ± 1.2#	39.6 ± 1.1
IENFD (no./mm)	9.7 ± 0.8	9.5 ± 0.7	5.8 ± 0.9*	4.9 ± 0.9	5.4 ± 0.93*	5.7 ± 1.1
CNFD (no./mm^2)	29.8 ± 1.2	29.2 ± 1.9	20.1 ± 1.6#	18.6 ± 1.8	16.8 ± 2.0#	19.4 ± 2.6~
CNBD (no./mm^2)	39.6 ± 2.5	40.2 ± 4.4	23.5 ± 2.7#	20.9 ± 2.9	17.6 ± 2.4#	25.4 ± 3.7~
CNFL (mm/mm^2)	17.4 ± 0.6	17.3 ± 0.9	12.2 ± 0.8#	11.9 ± 0.9	10.1 ± 1.0#	12.2 ± 1.1^

Data are expressed as mean ± SEM. eGFR, estimated glomerular filtration rate; NDS, neuropathy disability score; NSP, neuropathy symptom profile; PMNA, peroneal motor nerve amplitude; PMNCV, peroneal motor nerve conduction velocity; SNAP, sural nerve action potential; SNCV, sural nerve conduction velocity. All symbols represent statistically significant differences using one-way ANOVA: *$P < 0.005$, #$P < 0.0001$, baseline vs. control; ~$P < 0.05$, ^$P < 0.005$, baseline vs. 24 months.

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