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Near normoglycaemia improved nerve conduction and vibration sensation in diabetic neuropathy

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Summary. Twelve C-peptide deficient Type 1 (insulin-dependent) diabetic patients with abnormal peripheral nerve function were randomly assigned to continuation of conventional insulin therapy (CIT) or to continuous subcutaneous insulin infusion (CSII). There were no statistically significant differences at entry to the study between the two treatment groups in nerve function assessed by neurologic disability score, computer assisted sensation examination and measurements of amplitudes, distal latencies, F-wave latencies and somatosensory evoked potential latencies over the spine and conduction velocities of motor and sensory fibers of ulnar, median, peroneal, tibial, plantar and sural nerves. In addition, mean plasma glucose from 24 h profiles (12.5 vs 10.6 mmol/l, respectively) and HbA_1 (11.0 vs 11.6%, respectively) did not differ significantly between the two treatment groups at entry. Despite improved glycaemia from CSII in 5 patients (one dropped out of the study after 2 months) contrasted to CIT in 6 patients (5.3 vs 9.9 mmol/l, respectively, $p = 0.002$) and HbA1 (8.5 vs 10.7%, respectively, $p = 0.002$), there were no significant differences in measurements of peripheral nerve function after 4 months. After 8 months of improved glycaemia (4.4 vs 10.2 mmol/l, $p = 0.004$) and improved HbA_1 (8.3 vs 10.5%, $p = 0.002$), nerve conduction ($p = 0.03$) and vibratory sensation threshold ($p = 0.002$) were significantly better in patients treated with CSII than those who received CIT. The improvements in nerve function, although small, provide further evidence that some clinical endpoints of neuropathy are favorably influenced by improved control of glycaemia.

Key words: Normoglycaemia, neuropathy, CSII, nerve conduction, sensation examination.

Evidence is accumulating which implicates hyperglycaemia as a factor in diabetic peripheral neuropathy. Abnormal nerve conduction [1, 2, 3] and clinical neuropathy [2, 3, 4] in human diabetes have been associated with poor metabolic control. In addition, some measurements of peripheral nerve function in man have been observed to improve after weeks or months of improved glycaemia [4–16]. However, the significance of these latter observations is difficult to assess because most studies were uncontrolled and measurements were made of only a few parameters of nerve conduction in a few nerves.

It is not known whether improvement in nerve function requires partial or total correction of hyperglycaemia and what duration of therapy is needed. Neither maintenance of normoglycaemia for 3 days using an artificial endocrine pancreas [17] nor partial correction of hyperglycaemia for 2 years in a prospective randomized clinical trial resulted in improved peripheral nerve function [18].

We report here the results from a prospective randomized clinical trial in which the effects of near normoglycaemia on peripheral nerve function in Type 1 (insulin-dependent) diabetic patients were examined. These patients were part of a multicenter clinical trial which examined the effect of near normoglycaemia on nonproliferative retinopathy [19].

Subjects and methods

Patients

Twelve Type 1 (insulin-dependent) C-peptide deficient (basal, 0.015 ± 0.008 pM/ml; 6 min after intravenous glucagon, 0.016 ± 0.007 pM/ml) diabetic patients volunteered for study. Subjects were excluded if there was any evidence on detailed neurologic examination and laboratory evaluation for a cause for neuropathy other than diabetes. Their clinical features are shown in Table 1. The study was approved by the Institutional Review Board of the Mayo Clinic; each patient provided written informed consent. Patients were randomly assigned either to continuation of conventional insulin therapy (CIT) or to continuous subcutaneous insulin infusion (CSII) using a portable insulin infusion pump [18]. One patient, a male aged 26 years, assigned to CSII dropped out of the study after 2 months.

Each patient's diet was reviewed by the General Clinical Research Center dietitian to ensure full understanding of the principles of a

Table 1. Clinical features of patients at entry to the study

Patient	Age (yrs)	Gender	BMI	Diabetes duration (years)	Insulin treatment	HbA1 (%)	Mean plasma glucose (mmol/l)	Serum creatinine (μmol/l)	Urine protein (mg/24 h)	Retinopathy
Continuous subcutaneous insulin infusion (CSII)										
1	33	F	17.4	8	L20	15.7	11.9	70.7	82	MA
2	29	M	29.4	6	L60R5	11.4	12.3	79.6	49	MA
3	41	M	25.7	16	L40R12,R12	10.2	7.8	159.1	574	MA+H
4	38	F	22.8	27	L15R5,L15R5	10.5	12.8	88.4	34	MA+H
5	17	F	23.8	10	N25R10,R10	12.9	11.9	79.6	25	MA
6[a]	26	M	26.8	13	N60	9.1	7.0	79.6	74	MA+H+SE
x	30.7		24.3	13.3		11.6	10.6	92.8	139.6	
SEM	3.5		1.2	3.1		1.0	1.0	13.4	87	
Conventional insulin treatment (CIT)										
1	33	F	26.6	30	L46	9.8	12.1	79.6	84	MA+IRMA
2	38	M	32.1	16	N40,N22	13.6	12.9	97.2	113	MA+HE
3	49	M	26.0	27	R7S8,R6S6U6	8.4	13.2	97.2	127	MA
4	28	F	22.9	18	L60	11.5	9.5	70.7	67	MA
5	24	F	26.4	10	L50	9.6	12.2	70.7	52	MA
6	25	M	23.8	11	L54	12.8	15.2	79.6	22	MA
x	32.8		26.3	18.7		11.0	12.5	82.5	78	
SEM	3.9		1.3	3.4		0.8	0.8	4.9	16	
p	NS		NS	NS		NS	NS	NS		

[a] patient dropped out after 2 months
L = Lente insulin; R = regular insulin; N = NPH insulin; S = Semi-lente insulin; MA = microaneurysm; H = hemorrhage; SE = soft exudate; HE = hard exudate; IRMA = intraretinal microvascular abnormality

weight maintenance American Diabetes Association diet. Patients were instructed to eat 3 meals and a bedtime snack daily. The CIT patients were treated with their customary insulin therapy: 4 patients took one injection and 2 patients two injections of insulin daily.

CSII was initiated as previously described [20]. CSII patients were fully instructed in the technique of self-monitoring of blood glucose using a Glucometer (Ames Division of Miles Laboratories, Elkhart, IN, USA) and urged to measure blood glucose at least 4 times daily preprandially during the 8 months of study. The CSII patients were in frequent telephone contact with the investigators for assistance in insulin adjustment. Each CSII patient returned at least monthly for follow-up.

Data collection

Each patient underwent a 24-h period of inpatient plasma glucose monitoring in the General Clinical Research Center at entry to the study and again at 4 and 8 months. Blood was withdrawn at: 08.00, 09.00, 09.30, 10.00, 11.00, 12.00, 13.00, 13.30, 14.00, 15.00, 16.00, 17.00, 18.00, 18.30, 19.00, 21.00, 22.00, 24.00, 04.00, 06.00 and 08.00 hours. In addition, all patients collected capillary blood specimens (250 μl) into fluoride heparin tubes (Sarstedt Co., Princeton, NJ, USA) at home before and 90 min after meals and before the bedtime snack on one day each month. These samples were maintained at 4 °C prior to analysis for glucose at the General Clinical Research center. Haemoglobin Al was determined every 2 months. Detailed records were kept of untoward reactions, hypoglycaemia, ketoacidosis, and pump malfunctions.

Analytical methods

Blood (outpatient-collected) or plasma (inpatient-collected) glucose was measured on a YSI (Model 23A) (Yellow Springs Instruments, Yellow Springs, OH, USA) glucose analyzer. Diurnal glucose values were expressed as the mean and the M-value of Schlichtkrull et al. [21] as modified by Service et al. [22]. Blood collected for HbA1 was preincubated to remove the labile component then measured using Isolab minicolumns [23]. The range for nondiabetic persons is 5.5 to 7.5% with a coefficient of variation of 3.3%. C-peptide was determined as previously described [24]. Urine protein was measured by the method of Bradford [25].

At entry, 4 months and 8 months, each patient was examined by the same neurologist to generate a Neurologic Disability Score [26], and underwent Computer Assisted Sensation Examination (CASE) of the detection threshold of touch pressure, vibration of the great toe and cooling sensation of the foot. Abnormality for the first two modalities is expressed as the number of insensitive points (of 9 grid points tested) and as threshold of sensitive points. Abnormality of cooling sensation is expressed as threshold value [27]. Normal values have been published for the sites tested [28]. Electrophysiologic testing was performed by a single electromyographer (JRD). Action potential amplitudes, distal latencies, F-wave latencies, somatosensory evoked potential latencies over the spine and conduction velocities were recorded from motor and sensory fibers of multiple limb nerves (ulnar, median, peroneal, tibial, plantar and sural). The details of these techniques have been previously reported [29].

Statistical analysis

Statistical analysis was performed using nonparametric methods (median values and rank sum tests) for all data except CASE measurements because of the distinctly nongaussian nature of the data. More powerful parametric methods (mean and two sample t-tests) were used for evaluating CASE data. Analyses were two-tailed for comparisons at baseline. However, since the study was designed to address the one-sided question, "Does CSII improve diabetic polyneuropathy relative to CIT?", comparisons at follow-up were based on the corresponding one-sided tests.

It was anticipated that, in view of the large number of nerve conduction variables measured, some comparison between groups might be found to be statistically significant (i.e. p less than 0.05) by chance. In order to supplement conventional univariate analyses and obtain a single, overall, objective probability statement, an overall comparison of EMG measurements was undertaken using an adjusted ranking procedure [30]. For each variable, ranks were assigned to the pooled patients. The mean rank was then subtracted to obtain an adjusted rank. The corresponding adjusted ranks generated for each variable were summed for each patient, and a 2-sample t-test was performed on the summed adjusted ranks.

Since the electrophysiologic testing measures different aspects of nerve function which may respond to normalization in different ways, subsets of the nerve conduction measurements were analyzed separately: motor, sensory, lower extremities, distal, proximal, more abnormal at entry (> 15% deviation from mean) which included primarily ulnar and peroneal nerve measurements, and most reliable (< 5% variation in measurements) which included F-wave latency and conduction velocity measurements. The decision was made prior to data analysis that this subgroup analysis would be performed only if the results of the overall analysis were statistically significant.

Results

Glycaemic control

There were no significant differences ($p > 0.10$) in glycaemia or HbA1 between CSII and CIT at entry to the study (Table 2). Glucose control during the study was significantly better in CSII than CIT with restoration of glycaemia and HbA1 near the nondiabetic range both after 4 months (5.3 vs 9.9 mmol/l, and 8.5 vs 10.7%, respectively, $p = 0.002$) and after 8 months (4.4 vs 10.2 mmol/l and 8.3 vs 10.5%, $p = 0.004$, respectively). However, complete normalization of glycaemia was not achieved as the M-value in CSII (although significantly improved over CIT, 26 vs 60, respectively, $p = 0.002$) exceeded that observed in nondiabetes [17].

Table 2. Glycaemic control during the study[a]

	Glucose (mmol/l)		HbA1, %	*n*
	Inpatient, 4+8 months	Outpatient 1 through 8 months		
Conventional insulin therapy (CIT)	9.3	10.2	10.5	6
Continuous subcutaneous insulin infusion (CSII)	6.4	4.4	8.3	5
p-value[b]	0.041	0.004	0.002	

[a] Glucose data are expressed as the median value for each treatment group derived from the median value of the multiple mean 24-h glucose data of each patient. Similarly, a median value of HbA1 was generated from the multiple HbA1 determinations for each patient. The median for each treatment group is shown. [b] CIT vs CSII, rank sum test

The improvement in blood glucose control in the CSII group was associated with more episodes of hypoglycaemia than in the CIT group. Mild hypoglycaemia, defined as episodes which patients treated themselves, occurred at the rates (median per patient per month) of 8 and 0.5 ($p < 0.01$) for CSII and CIT, respectively. The rates for moderate hypoglycaemia, defined as episodes which required the assistance of others, were 0.9 and 0 ($p < 0.02$) for CSII and CIT, respectively. Hypoglycaemic episodes of such severity to require intravenous glucose or injection of glucagon occurred on three occasions for the patients in CSII and not at all for the patients in CIT. Our observation of increased incidence of hypoglycaemia during CSII in contrast to conventional insulin treatment is consistent with some reports [31, 19, 32] but not others [33–36]. Factors which may account for this discrepancy are differing intensity of ascertainment of hypoglycaemia between treatment groups and variable differences in glycaemic control and probably different degrees of insulinoprivia of patients from study to study. Diabetic ketoacidosis did not occur in any patient in CIT but occurred on one occasion in four patients in CSII as a result of pump malfunction and/or patient error. A proclivity to ketoacidosis during CSII has been noted by others [19, 34].

Peripheral Nerve Function

At entry to the study each of the eleven patients who completed the study had mild diabetic polyneuropathy based on recently established criteria [35]. Baseline neurologic assessments were not significantly different between CIT and CSII patients with regard to neurologic disability score (14 vs 16, respectively), number of abnormal nerve conduction measurements per patient (3.5 vs 4, respectively) expressed as median values, and computer assisted sensation examination: touch-pressure (0.2 ± 0.2 vs 0.6 ± 0.5 insensitive points, respectively; and 6.3 ± 0.2 vs 6.4 ± 0.5 1n mg, respectively, detection thresholds); vibration (0.8 ± 0.7 vs 4.0 ± 1.3 insensitive points, respectively; and 3.7 ± 0.1 vs 3.9 ± 0.1 1n μm, re-

Table 3. Changes in computer assisted sensation examination

	Conventional insulin therapy (CIT) ($n = 6$)			Continuous subcutaneous insulin infusion (CSII) ($n = 5$)			
	Baseline	8 month	Difference[b]	Baseline	8 month	Difference[b]	p[a]
Touch pressure							
No of points insensitive	0.2	0	0.2	0.6	1.0	−0.4	0.600
Threshold, 1n mg	6.3	6.2	0.1	6.4	6.3	0.1	0.510
Vibration							
No of points insensitive	0.8	1.1	−0.3	4.0	1.6	2.4	0.002
Threshold, 1n μm	3.7	4.0	−0.3	3.9	3.7	0.2	0.105
Cooling threshold for temperature change (°C)	4.6	5.6	−1.0	5.8	6.5	−0.7	0.465

[a] t-test. [b] baseline minus 8-month values

Table 4. Magnitude of changes from baseline in nerve conduction at 8 months[a,b]

	Conventional insulin therapy (CIT) ($n=6$)	Continuous subcutaneous insulin infusion (CSII) ($n=5$)
Conduction velocity m/s		
Motor	0.13	1.42[c]
Sensory	0.04	4.08[c]
Amplitude		
Motor mv	0.03	−0.25
Sensory uv	−0.75	0[c]
Distal latency (ms)		
Motor	−0.05	−0.25[c]
Sensory	−0.03	−0.25[c]
F-wave latency (ms)	0.25	−2.25[c]
SEP latency (ms)	−0.17	−1.38[c]

[a] Baseline minus 8 month values; [b] median value; [c] better function in CSII than CIT

Table 5. p = values for differences in subsets of nerve conduction parameters[a]

Conventional insulin therapy (CIT) vs continuous subcutaneous insulin infusion (CSII)	
Proximal function	0.001
Most reliable	0.029
Speed of conduction	0.044
Sensory nerves	0.045
Lower extremity	0.156
Most abnormal initially	0.156
Distal function	0.164

[a] Adjusted rank scores of change from entry values, analyzed by student's t-test

spectively, detection threshold); cooling (4.6 ± 1.7 vs 5.8 ± 1.7 °C, respectively) expressed as M ± SEM.

Mean values for all nerve conduction parameters for all patients were abnormal ($p < 0.01$ vs age-matched normal subjects) at entry, with no significant differences between CIT and CSII patients. The abnormalities were greatest for sensory nerve action potential amplitudes which were reduced 40–80% below the normal mean. In addition, all nerve conduction parameters differed from the normal mean by 10–20%. Both treatment groups were generally homogeneous with mildly abnormal or borderline values in a number of nerves. Scattered fibrillation potentials were seen in foot and paraspinal muscles in a few patients, but motor unit potential abnormalities were present in all but one, with no differences between the two treatment groups.

Despite significant differences in glycaemic control between CIT and CSII, with better control in the latter over the first 4 months of study, there were no significant differences ($p > 0.10$) in any of the parameters of peripheral nerve function at 4 months.

After 8 months of significantly better glucose control in CSII than CIT there were no statistically significant ($p > 0.10$) differences in neurologic disability scores between CIT and CSII. However, of the CASE measurements there was a significant ($p = 0.002$) difference in change from baseline values of the number of points insensitive to vibration (Table 3). CSII patients showed a reduction in number of points insensitive (2.4), whereas the CIT patients had a slight increase in number of points insensitive (−0.3). Furthermore, the threshold of vibratory sensation of sensitive points improved in CSII (+0.2 1n μm) and worsened (−0.3 1n μm) in CIT.

Of the 34 parameters of nerve conduction measured, differences between CIT and CSII were observed in 30 with the better function observed with CSII in 26 and with CIT in 4. The adjusted rank score analysis showed statistically significant better function in CSII than CIT at 8 months ($p = 0.03$) but no difference at 4 months.

Despite very small sample sizes, statistically significant differences between CIT and CSII were observed for median motor F-latency ($p = 0.026$), sural sensory peak latency at 13 cm. ($p = 0.018$), and median somatosensory evoked potential latency at the neck ($p = 0.002$), with the better function observed in CSII in each case. The advantage for CSII was of borderline significance for plantar sensory peak latency at 11 cm. ($p = 0.057$), and suggestive significance for peroneal motor conduction velocity ($p = 0.063$), median motor distal latency ($p = 0.089$), peroneal motor F-latency ($p = 0.067$) and tibial motor distal latency ($p = 0.089$) when CSII was compared to CIT.

The magnitudes of change in nerve conduction measurements from baseline for the various parameters were not large (Table 4). Analysis by adjusted rank scores of subsets of nerve conduction parameters showed statistically significant differences between CIT and CSII with better function in the latter for measures of proximal function ($p = 0.001$), most reliable parameters ($p = 0.029$), speed of conduction ($p = 0.044$), and those of sensory nerves ($p = 0.045$). No statistically significant differences ($p > 0.10$) were noted for other subsets (Table 5).

Discussion

Whether improved glycaemia can prevent or ameliorate the neuropathy of diabetes cannot be determined unequivocally from published reports. However, there is highly suggestive evidence that better blood glucose control at least partially improves such expressions of neuropathy as abnormalities of nerve conduction and vibratory threshold.

We reasoned that a demonstration of the benefit of control of hyperglycaemia on nerve function would require a prospective clinical trial and the use of sensitive and reliable neuropathic endpoints. The present study had the following favourable characteristics: (1) recruitment was limited to Type 1 diabetic patients who were homogeneous clinically, were uniformly C-peptide defi-

cient and had mild neuropathic dysfunction; (2) a control group of patients receiving conventional insulin therapy was included; (3) there was random assignment of patients to conventional and intensive insulin therapy; (4) the patients in the two treatment groups were comparable at entry by metabolic and neuropathic dysfunction criteria; (5) a large and highly significant difference in glucose control was achieved between the 2 treatment groups; (6) the study was prospective, lasting 8 months; and (7) the neuropathic dysfunction was broadly assessed by using various measures of clinical neuropathic dysfunction and many parameters of nerve conduction.

This study has shown small but statistically significant improvements in vibration sensation and nerve conduction parameters by 8 months but not by 4 months in the CSII treated patients. Although these improvements were small and took a long time to develop, we believe they reflect improvement in polyneuropathy. This opinion is based on several reasons: (1) statistical improvement was found in two independent evaluations (nerve conduction and vibratory threshold); (2) by the design and nature of both tests, observer and patient bias should not have accounted for the improvement; (3) among the three sensory thresholds employed, vibration is the most sensitive at detecting sensory abnormality in diabetic polyneuropathy [35] and possibly the most likely to improve; and (4) severity of the abnormality of nerve conduction and of vibratory threshold has been found to be significantly associated with the severity of fiber loss [37]. Does the demonstrated improvement reflect metabolic or structural alterations, and is the magnitude of the change sufficiently large to be clinically important? The first question cannot be answered because nerve tissue was not studied. The improvement in vibratory threshold (decreased numbers of insensitive points and improvement in threshold of sensitive points) provide direct evidence of clinical improvement, albeit of small magnitude.

Theoretical reasons for the small magnitude of improvement in nerve function resulting from the improved glycaemia include: (1) nerve dysfunction was not present initially; therefore, improvement would not be expected; (2) damaged nerves cannot improve; (3) too few subjects were studied; (4) complete normalization of glycaemia was not achieved; (5) insufficient duration of the study. Many of these reasons appear unlikely to apply to the current study. Nerve function was abnormal at entry and nerve function has been shown to improve after various injuries [38, 39]. Although more patients and a longer trial would have been desirable, small groups of patients with other types of neuropathy, e.g. myxedema neuropathy and uremic neuropathy, have been shown to improve unequivocally by the parameters of nerve function used in this study following treatment over durations comparable to that of the current study [38, 40]. After considering all these factors, the hypothesis most consistent with the results of this study is that either the effect of near normoglycaemia is indeed small or that it takes a long time for this effect to develop. The improvement in nerve function observed at 8 months but not at 4 months supports the latter hypothesis and suggests that less easily reversible events may be interposed between correction of hyperglycaemia and the neuropathic changes. Small improvements in nerve function when extended over a long period of time may result in clinically evident improvement. Long-term studies in a large group of patients will be needed to determine the degree and duration of control of hyperglycaemia required to prevent or ameliorate different types and severities of diabetic neuropathy.

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