

Validation of the Toronto Clinical Scoring System for Diabetic Polyneuropathy

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OBJECTIVE— The aim of the current study was to determine the validity of the Toronto Clinical Scoring System (CSS) in reflecting the presence and severity of diabetic peripheral sensorimotor polyneuropathy (DSP) as determined by myelinated fiber density (FD) on sural nerve biopsy.

RESEARCH DESIGN AND METHODS— Eighty-nine patients with both type 1 and type 2 diabetes, ascertained from a large therapeutic randomized controlled trial, were included in this cross-sectional, observational cohort study. Morphological severity of DSP was expressed as the FD in the sural nerve biopsy. The Toronto CSS was applied to all patients to determine a clinical neuropathy score. General linear regression models were used to assess the relationship between the morphological severity of DSP and the Toronto CSS.

RESULTS— The Toronto CSS showed a significant negative correlation with sural nerve FD ($R^2 = 0.256$, $P < 0.0001$). The Toronto CSS was lower in those with better glycemic control ($HbA_{1c} \leq 8\%$). Sural nerve FD and the Toronto CSS showed strong correlations with electrophysiology, by both summed amplitude and summed conduction velocity values.

CONCLUSIONS— The Toronto CSS is a valid instrument to reflect the presence and severity of DSP as measured by sural nerve morphology and electrophysiology. The results of the current study underscore the interrelationships between clinical deficits, electrophysiological findings, and morphological changes in DSP. This evidence suggests that the Toronto CSS may prove useful in documenting and monitoring DSP in the clinic and in clinical research trials.

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Diabetic peripheral sensorimotor polyneuropathy (DSP) is a frequent complication of both type 1 and type 2 diabetes. The pathological hallmark of DSP is progressive nerve fiber loss of both large and small fibers (1–3). Changes in sural nerve fiber density (FD) have been documented repeatedly as the major change underlying DSP (3–5). Correlations between morphological change and nerve function as determined by the results of nerve conduction studies (NCS) have been demonstrated previously for

DSP and other polyneuropathies (4,6). Similar relationships between NCS and quantitative sensory thresholds (7,8), as well as between NCS and the clinical features of neuropathy (9–11), are documented. Quantitative sensory thresholds (QSTs) also reflect the clinical severity of neuropathy as shown by the prediction of foot ulceration with vibration perception thresholds >25 V (12,13).

Both NCS and QST provide quantitative measures of peripheral nerve activity. Recently, different clinical scoring sys-

tems were developed as quantitative instruments to document the presence and severity of DSP (14–18). None of these instruments has been validated against morphological criteria for DSP. The Toronto Clinical Scoring System (CSS) was implemented in another study of simple screening methods for DSP to stratify patients into severity categories and correlated well with NCS findings and complications in subjects with DSP in that study (18). It was consequently hypothesized that the Toronto CSS could be considered a simple method for evaluation of DSP. Further validation in patients with documented DSP was required.

The aim of the current study was to examine how well the Toronto CSS correlates with the presence and severity of DSP as determined by electrophysiological criteria and the additional morphological gold standard of myelinated FD on sural nerve biopsy in an independent group of DSP patients.

RESEARCH DESIGN AND METHODS

Eighty-nine patients with diabetic DSP were included in this cross-sectional survey of a cohort study. The Toronto CSS was applied retrospectively to this group. These patients were initially enrolled in a double-blind, randomized, placebo-controlled trial of the effects of acetyl-L-carnitine in patients with clinical and electrophysiological criteria for DSP with normal renal function (6). This group represents an unselected cohort of patients with DSP as defined below. All data were collected before randomization and initiation of treatment with the active study drug or placebo. The study was approved by the Toronto General Hospital (University Health Network) Research Ethics Board. Criteria for selection into the randomized controlled trial included patients with type 1 or 2 diabetes; $HbA_{1c} \geq 5.9\%$ by affinity chromatography at screening; peripheral neuropathy diagnosed by abnormalities in two of four major categories (symptoms, signs, NCS, and quantitative sensory testing); and the presence of bilateral sural potentials ≥ 1 μ V. Patients with peripheral neuropathy with principal causes

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Abbreviations: CV, conduction velocity; DSP, diabetic peripheral sensorimotor polyneuropathy; FD, fiber density; NCS, nerve conduction studies; QST, quantitative sensory threshold; SUMAMP, sum of lower-limb distal amplitudes; SUMCV, sum of lower-limb nerve conduction velocities; Toronto CSS, Toronto Clinical Scoring System.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Toronto Clinical Neuropathy Scoring System

Symptom scores	Reflex scores	Sensory test scores
Foot	Knee reflexes	Pinprick
Pain	Ankle reflexes	Temperature
Numbness		Light touch
Tingling		Vibration
Weakness		Position
Ataxia		
Upper-limb symptoms		

Sensory testing was performed on the first toe. Symptom scores: present = 1; absent = 0. Reflex scores: absent = 2; reduced = 1, normal = 0. Sensory test score: abnormal = 1, normal = 0. Total scores range from normal = 0 to maximum of 19.

other than diabetes—such as alcohol abuse; liver or renal disease; toxic exposure; endocrine, metabolic or nutritional disorders; inflammatory diseases; or monoclonal gammopathies—were excluded from the present study.

The Toronto CSS was developed initially for use in another study of simple screening tests for DSP in the clinic (18). It was designed as a simple way to stratify patients to ensure that a diverse population with a broad spectrum of DSP entered the study with a minimum number of 50 subjects per group. The Toronto CSS was based on classic neurological history and examination techniques and designed to be simple and relevant to the clinician. Elements were chosen for the Toronto CSS by local expert opinion based on a consensus of neurologists and diabetologists. Variables were kept dichotomous to ensure simplicity, other than deep tendon reflexes, which carried additional weight. The Toronto CSS was applied to all patients in the current study by an observer blinded to the results of the NCS and sural nerve biopsy findings. The Toronto CSS, shown in Table 1, is weighted to emphasize sensory symptoms and deficits, the first features typically observed in DSP. Each patient was questioned as to the presence or absence of pain (characteristic of neuropathic pain such as burning, stabbing, or shock-like), numbness, tingling, and weakness in the feet; the presence or absence of similar upper-limb symptoms; and the presence or absence of unsteadiness on ambulation. Sensory testing was performed at the first toe and rated as normal or abnormal. The outcome, the clinical neuropathy score, is a continuous variable ranging from a minimum of 0 (no neuropathy) to a maximum of 19 points. Six points are derived from symptoms, eight from low-

er-limb reflexes, and five from sensory examination distally at the toes. In the previous study (18), the Toronto CSS outcome variables were normally distributed in 428 subjects with diabetes and a broad range of DSP (skewness -0.522). The mean values were, for healthy volunteers, 0.63 ± 1.3 ; nonneuropathic subjects with diabetes, 4.0 ± 2.6 ; mild DSP, 5.0 ± 1.1 ; moderate DSP, 8.2 ± 0.8 ; and severe DSP, 10.9 ± 0.9 .

Reproducibility of the Toronto CSS was tested subsequently in another group of 10 subjects. Each patient was assessed on the same day by three different examiners kept blinded to the results of the other tests. The subjects were also tested on three different days by the same examiner. The intra-observer variability (same subject tested by the same examiner on three different days) was 7.3%, and the interobserver variability (same subject tested by three different examiners on the same day) was 6.3% on repeat testing.

Standard nerve conduction studies of the nondominant median motor and sensory nerves, dominant peroneal motor nerves, and sural nerves were performed on all subjects using the Counterpoint instrument (Medtronic, Mississauga, Canada). Recordings were performed with temperature control ($32\text{--}34^\circ\text{C}$), careful distance measurements, and recording of well-defined and artifact-free responses. Surface silver/silver chloride discs with a standardized size of 4×7 mm were used to record all nerve responses. Three nerve conduction studies were done within 2–3 weeks. Latencies and amplitudes were determined automatically, distance values were entered into the Counterpoint, and conduction velocities were calculated automatically. The mean values of repeat nerve conduction velocities (CVs) and amplitudes were calculated. Only lower-

limb nerve conduction study results were used in the analyses to compare directly with sural nerve morphological parameters. SUMCV (sum of lower-limb nerve conduction velocities) and SUMAMP (sum of lower-limb distal amplitudes) are composite variables created from the three examined nerves in the lower limb.

Full-thickness sural nerve biopsies were performed at an anatomical location posterior to the lateral malleolus by an experienced and protocol-trained surgeon. The biopsies were done using local anesthetic (1% lidocaine without epinephrine). A 7-cm segment of nerve was obtained with care to avoid tension on the nerve, then sectioned and prepared for analysis. A portion was fixed with glutaraldehyde, and another portion was frozen with dry ice and shipped to a central laboratory where the portions were recoded for blinded analysis. The nerve segments were postfixed in 1% osmium [4% sucrose, 1.5% $\text{K}_3\text{Fe}(\text{CN})_6$ in cacodylate buffer], dehydrated through ethanol (50–100%), and placed in propylene oxide before embedding in Epon 812 such that the cut faces of the nerve incised at the time of biopsy were oriented toward the face of the block. After curing, $1\text{-}\mu\text{m}$ sections were cut and stained with paraphenylenediamine to enhance the contrast of myelin for quantitative computer-assisted light microscopic morphometric analysis. The largest fascicle meeting criteria from cross-sectional area ($\geq 100,000 \mu\text{m}^2$), fixation, and mechanical distortion ($\leq 6\%$ endoneurial area) was selected for light microscopic morphometric analysis. The selected fascicle was digitally imaged at $400\times$ and analyzed for total endoneurial area, number of myelinated fibers, and total axon areas of each myelinated fiber by a semiautomated image analysis system. The fiber count (all fibers in the fascicle) and fascicular area (in square micrometers) were determined. Fascicular fiber density was obtained in the standard manner by dividing the total fiber count by total fascicular area and multiplying by 1,000,000. The value is expressed in fibers per square millimeter.

HbA_{1c}, cholesterol, and triglycerides were measured using routine biochemical tests.

Statistical evaluation was performed with Statview 5.0 (SAS, Carey, NC) software for Macintosh. The Toronto CSS was normally distributed, with a mean value of 11.54 ± 2.8 , skewness -0.245 . The

Table 2—Demographic characteristics of 89 patients with diabetic DSP

Total number of patients	89
Male/female	65/24
Type 1/type 2 diabetes	18/71
Age (years)	54.2 ± 10.2
Diabetes duration (years)	11.2 ± 8.8
DSP duration (years)	2.9 ± 3.8
HbA _{1c}	8.5 ± 1.7
Retinopathy (%)	26
Nephropathy (%)	2
Hypertension (%)	44
Erectile dysfunction (% males)	58
Smokers (%)	51
Coronary artery disease (%)	26
Vibration perception threshold (vibration units)	
Finger	1.2 ± 0.9
Toe	4.7 ± 3.2
Mean myelinated fiber density	3,025.784 ± 1,912.132
Peroneal motor amplitude (mV)	3.7 ± 2.3
Peroneal motor CV (m/s)	37.7 ± 5.5
Sural amplitude (μV)	4.6 ± 3.2
Sural CV (m/s)	38.3 ± 5.8

Data are means ± SD.

summed sural CV was normally distributed, with a mean of 76.9 ± 10.7 , skewness -0.215 . The summed amplitude score was normally distributed, with a mean of 11.6 ± 6.7 , skewness 0.400 . In univariate analyses, Pearson's coefficient of correlation between the FD (gold standard) and Toronto CSS was calculated. The FD values within categories of DSP severity, as defined by the Toronto CSS, were analyzed by ANOVA. The same results were expected for the correlation between the Toronto CSS and NCS as observed in a previous study (18). Consequently, exploratory analyses included linear regression analysis between summed NCS results and the Toronto CSS. Multiple linear regression and logistic regression modeling were used to control for the effects of multiple variables. Student's *t* test was used for two-group comparisons. Reproducibility was assessed by percent variation on repeat testing.

RESULTS—The study group included 65 men and 24 women. The demographic profile is shown in Table 2. Seventy-one patients were diagnosed as having type 2 and 18 subjects as having type 1 diabetes. The mean age (\pm SD) of patients was 54.2 ± 10.2 years, the mean diabetes duration was 11.2 ± 8.8 years, and the mean duration of symptoms of

neuropathy was 2.9 ± 3.8 years. The mean HbA_{1c} was $8.5 \pm 1.7\%$.

The relationship between the severity of DSP as provided by the Toronto CSS and the sural nerve FD was investigated by univariate correlation analysis. The Pearson correlation for the total Toronto CSS and FD was 0.466 ($P < 0.0001$). The different elements of the Toronto CSS showed significant correlations with the FD, as shown in Table 3. The FD was significantly and inversely correlated with the Toronto CSS (Fig. 1). Multiple linear regression analyses including age, duration of diabetes, and HbA_{1c} as independent variables confirmed the correlation between myelinated FD and the Toronto CSS ($R^2 = 0.229$, $P = 0.004$). If severity of DSP and glycemic control were considered as dichotomous variables (mild-moderate or severe for DSP and good versus poor control), logistic regression

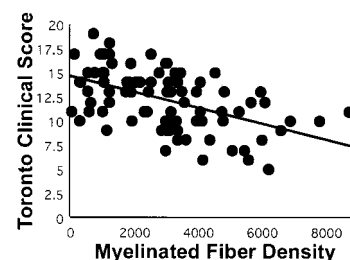


Figure 1—Toronto CCS versus myelinated FD in the study patients.

modeling confirmed the relationship between FD and severity of DSP (likelihood ratio test $\chi^2 = 7.167$, $P = 0.0074$) (Fig. 2) and also showed a relationship between glycemic control and severity of DSP (likelihood ratio test $\chi^2 = 5.931$, $P = 0.0149$).

The relationships between the Toronto CSS and SUMAMP and SUMCV show significant inverse correlations ($R = 0.424$, $P < 0.0001$; $R = 0.302$, $P = 0.0044$). Different components of the Toronto CSS related to the NCS variables are shown in Tables 4 and 5. Individual elements of the Toronto CSS did not separate the FD, other than normal/abnormal deep tendon reflexes such that those with abnormal reflexes had significantly lower FD ($2,827.1 \pm 1,897.9$ vs. $4,006.8 \pm 1,574.8$; $P = 0.0444$), and those with ataxia had a lower FD ($1,754.4 \pm 1,041.0$ vs. $3,115.0 \pm 1,918.8$) of borderline significance ($P = 0.0522$). The presence of numbness tended to increase with decreasing FD ($2,904.4 \pm 1,896.7$ vs. $3,833.5 \pm 1,746.1$), but did not reach statistical significance ($P = 0.1875$). Those with pain due to DSP did not have a significantly different FD. Those without neuropathic pain had a lower mean number of axon clusters (20.5 ± 17.1 vs. 12.4 ± 14.8), but this difference did not reach statistical significance. The total number of axons and axon density did not differ between subjects depending on the

Table 3—Univariate correlation coefficients for the relationship between fiber density and the components of the Toronto CSS

	Correlation coefficient (Pearson)	P	Correlation coefficient (Spearman)	P
Symptom scores	0.203	0.0583	-0.182 (-1.700)	0.0892
Reflex scores	0.458	<0.0001	-0.406 (3.742)	0.0002
Sensory test scores	0.175	0.1030	-0.061 (-0.566)	0.5711
Total Toronto CSS score	0.489	<0.0001	-0.479 (-4.417)	<0.0001

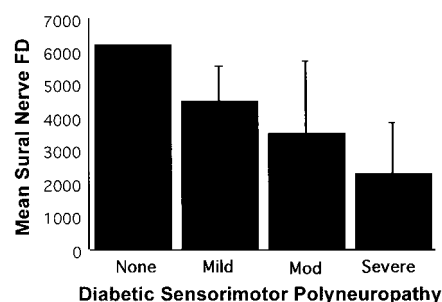


Figure 2—Correlation of mean sural nerve FD with diabetic sensorimotor polyneuropathy. Error bars, ± 1 SD.

presence of pain. Of great interest is the finding that those with numbness had fewer axon clusters than those without (51.5 ± 59.8 vs. 164.7 ± 110.8 ; $P = 0.0077$).

When glycemic control was considered as a dichotomous variable (those having HbA_{1c} values $\leq 8\%$ vs. those with values $>8\%$), the Toronto CSS was significantly lower in those with poor control (mean fiber density $3,556 \pm 2023$ compared with $2,626 \pm 1,727$; $P = 0.0244$) (Fig. 3). When glycemic control was considered as a continuous variable, a significant correlation between HbA_{1c} and sural nerve myelinated FD was observed ($R^2 = 0.102$, $P < 0.019$).

The relationships between the FD and SUMAMP and SUMCV have been presented previously (6).

CONCLUSIONS—The present study has shown that clinical neuropathy as characterized by the Toronto CSS is related to the morphological severity of DSP. This relationship was shown in both univariate correlation analysis and in multivariate analysis using general linear modeling, thus controlling for potential confounding variables. The overall severity of diabetic DSP was expressed by using

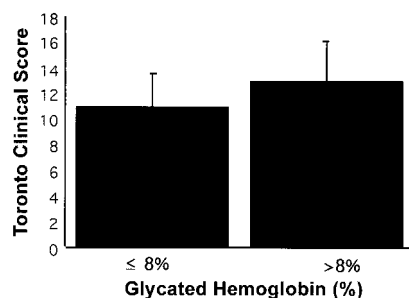


Figure 3—Correlation of Toronto CSS with HbA_{1c}. Error bars, ± 1 SD.

Table 4—Univariate correlation coefficients for the relationship between summed amplitude NCS values and the components of the Toronto CSS

	Correlation coefficient (Pearson)	P	Correlation coefficient (Spearman)	P
Symptom scores	0.029	0.7897	0.003 (0.027)	0.9784
Reflex scores	0.484	<0.0001	−0.397 (−3.681)	0.0002
Sensory test scores	0.106	0.3211	−0.007 (−0.067)	0.9465
Total Toronto CSS score	0.424	<0.0001	−0.386 (−3.578)	0.0003

the Toronto CSS. In addition, HbA_{1c} was a significant independent predictor for the severity of neuropathy. Age failed to reach statistical significance, despite a trend toward increased severity with increasing age. The study is limited in that it is retrospective and done in a cohort of subjects with a limited spectrum of disease. It would be of interest to examine relationships between morphological changes and other clinical scoring systems, which was not possible in this group of patients (some of the information necessary to complete the other scores was not available in the patient records). A prospective study might be of interest, but the requirement for sural nerve biopsy would limit the feasibility of such an enterprise.

Although the Toronto CSS is driven by the deep tendon reflexes insofar as the sural nerve myelinated fiber density is concerned, modification of the system is not advocated, as it contains elements representative of small unmyelinated fiber function, which was not addressed in the current study.

HbA_{1c} as an index of long-term diabetes control has been shown to be related to the incidence and the prevalence of diabetic DSP in both cross-sectional and prospective epidemiological studies that primarily include patients with type 1 diabetes, such as the Pittsburgh Epidemiology of Diabetic Complications Study (19,20), the EURODIAB Type I Study (21), the Seattle Prospective Diabetic Foot

Study (22), the Diabetes Control and Complications Trial (23), and, most recently, the Rochester Diabetic Neuropathy Study cohort (24). The study by Tkac et al. (25) showed that HbA_{1c} was a modifiable risk factor for electrophysiological severity of diabetic DSP. Perkins et al. (6) demonstrated that HbA_{1c} is also a modifiable risk factor for severity of FD loss in diabetic DSP. This finding can now be extended to show that HbA_{1c} is related to the clinical features of DSP as measured by the Toronto CSS. Thus HbA_{1c} levels determine DSP as measured clinically, by surrogate markers (NCS and QST), and by morphological techniques. The interrelationships between clinical deficits, electrophysiological findings, and morphological changes in DSP are emphasized by the current study.

Two interesting further observations arise from this study. Subjects with numbness experience the same fiber density as those without numbness, and although a lower fiber density was observed, the difference was not significant. Furthermore, subjects without numbness were observed to have a larger number of axon clusters. These observations suggest that those with normal sensory perception have a more effective reinnervation process even though the severity of neuropathy as expressed by FD is comparable. The presence of more axon clusters protects against the sensory perception of numbness, indicating clinically relevant activity of the axon clusters. The

Table 5—Univariate correlation coefficients for the relationship between summed conduction velocity NCS values and the components of the Toronto CSS

	Correlation coefficient (Pearson)	P	Correlation coefficient (Spearman)	P
Symptom scores	0.124	0.2476	−0.054 (−0.511)	0.6096
Reflex scores	0.319	0.0026	−0.267 (−2.476)	0.0133
Sensory test scores	0.012	0.9098	−0.098 (−0.924)	0.3556
Total Toronto CSS score	0.302	<0.0044	−0.283 (−2.628)	0.0086

axon clusters do not impart a deleterious symptomatic effect, since those with painful DSP tended to have fewer axon clusters.

In summary, a major conclusion can be made from the present study. Clinical neuropathy characterized by the Toronto CSS correlates well with the underlying structural damage in peripheral nerve as shown by the loss of myelinated nerve fibers. This study adds further evidence that poor diabetes control is the most important factor related to the severity of diabetic peripheral sensorimotor neuropathy in patients with both type 1 and type 2 diabetes. Given that effective control of diabetes is beneficial for NCV in type 1 diabetes patients (26), it can be speculated that this type of intervention will have the same benefit on the Toronto CSS. The Toronto CSS may prove useful in documenting and monitoring DSP in the clinic and in clinical research trials.

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