Validation of a Novel Screening Device (NeuroQuick) for Quantitative Assessment of Small Nerve Fiber Dysfunction as an Early Feature of Diabetic Polyneuropathy

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OBJECTIVE — To validate a handheld screening device (NeuroQuick) for an early detection of diabetic distal symmetric polyneuropathy (DSP) by quantitative testing of cold sensation based on the wind chill factor (NeuroQuick threshold [NQT]).

RESEARCH DESIGN AND METHODS — NQT was measured on the dorsum of the foot in 160 healthy subjects as well as 60 and 128 diabetic patients without and with DSP, respectively. DSP was diagnosed by a neurological examination, motor and sensory nerve conduction velocity, vibration perception threshold, and warm and cold thermal perception threshold (TPT) (TPT Medoc). In addition, a C-64 Hz tuning fork and TipTherm device were used as screening instruments.

RESULTS — In the diabetic cohort, NQT correlated significantly with all nerve function tests, with the highest correlation coefficients being found on the foot versus Medoc warm TPT ($r = 0.618$, $P < 0.001$) and cold TPT ($r = 0.529$, $P < 0.001$). Among patients with DSP, NQT was abnormal, whereas Medoc warm TPT was normal in 34%, whereas only 5% showed the opposite constellation ($P < 0.05$). Likewise, the corresponding percentages for Medoc cold TPT were 32 and 11%, for TipTherm 47 and 2%, and for the tuning fork 29 and 10% (all $P < 0.05$), whereas no significant differences were noted when comparing NQT with peroneal motor nerve conduction velocity, sural sensory nerve conduction velocity, and malleolar vibration perception threshold. The coefficients of variation for repeated NQT measurements in 41 control and 41 diabetic subjects were 20.4 and 8.5%, respectively.

CONCLUSIONS — The NeuroQuick is a valid and reliable screening tool for quantitative assessment of small nerve fiber dysfunction. This device appears to be more sensitive in detecting early diabetic polyneuropathy than both elaborate thermal testing and screening tests such as the tuning fork.

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Abbreviations: DSP, distal symmetric polyneuropathy; MNCV, motor nerve conduction velocity; NQT, NeuroQuick threshold; SNCV, sensory nerve conduction velocity; TPT, thermal perception threshold; VPT, vibration perception threshold.

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

Distal symmetric polyneuropathy (DSP) is a frequent complication of diabetes affecting ~20–30% of the diabetic population (1). DSP is related to both lower-extremity impairment and functional limitations such as walking ability. There is accumulating evidence suggesting that nerve function tests indicating the presence of DSP such as impaired nerve conduction velocity and vibration perception threshold (VPT) predict mortality and the development of neuropathic foot ulceration, one of the most common causes for hospital admission, lower limb amputations, and economic burden in diabetic patients (2–6).

Small nerve fiber dysfunction, which is a frequent feature of DSP (7) affecting the Aδ- and C-fibers, can only be detected using time-consuming and expensive quantitative sensory testing equipment by measuring cold and warm thermal perception thresholds (TPTs) (8,9) or skin biopsy (10). Using the latter technique, shortening and loss of intra-epidermal nerve fibers in skin of the distal leg have recently been demonstrated in both diabetic and nondiabetic neuropathies (10).

Because the development of diabetic foot ulceration may be preventable by early detection of the underlying DSP, a number of simple screening instruments such as the Semmes-Weinstein monofilament (11,12), graduated Rydel-Seiffer tuning fork (13,14), tactile circumferential discriminator (15), or the Neuropen (16) have recently been recommended to identify the high-risk patient with DSP (17). However, these methods either provide categorical rather than quantitative results or assess large rather than small nerve fiber function. Because their information on the degree of severity of the neuropathic deficits or small fiber dysfunction is lacking or limited, their sensitivity in detecting early DSP is lower compared with quantitative sensory test-

ing or nerve conduction velocity (17). To overcome these limitations, we developed and validated an instrument (NeuroQuick) for quantitative bedside testing of cold TPT based on the wind chill factor, i.e., the effect that wind has on our perception of cold. This handheld microprocessor-operated electronic device comprises a fan adjustable to rotate at 10 different velocities, while a constant distance to the skin is ensured by laser diodes. Here we report the sensitivity, specificity, and reliability of this device compared with motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV), TPT, VPT, and two screening instruments.

RESEARCH DESIGN AND METHODS

— The diabetic subjects were recruited from the German Diabetes Clinic of the German Diabetes Center at the Heinrich Heine University, Düsseldorf. Inclusion criteria were type 1 or type 2 diabetes according to the World Health Organization/American Diabetes Association criteria. Informed consent was obtained from all subjects eligible to participate in the study after the procedures involved were fully explained. Exclusion criteria were as follows: *1*) neuropathy other than of diabetic origin, *2*) peripheral arterial disease (intermittent claudication or nonpalpable foot pulses), *3*) any medication that may adversely influence peripheral nerve function, *4*) neurological diseases (e.g., Parkinson's disease, multiple sclerosis), and *5*) blood glucose levels >400 mg/dl, symptomatic hypoglycemia, and/or ketonuria at the time of testing. Healthy subjects (n = 160) from homes for the elderly, students, and staff from the German Diabetes Center served as control subjects. Intraobserver reproducibility on 2 consecutive days was determined in healthy control subjects (n = 41, 20 men, 21 women, age 42.5 ± 13.3 years, BMI 23.9 ± 3.8) and diabetic subjects (n = 41, 24 men, 17 women, age 58.4 ± 14.9 years, BMI 30.7 ± 8.9). The investigations have been carried out in accordance with the principles of the Declaration of Helsinki, as revised in 2000.

Assessment of peripheral nerve function

Electrophysiological tests, thermal discrimination, and vibration perception thresholds were performed as previously described (7). MNCV was measured in the median and peroneal nerves, whereas SNCV was determined in the median and sural nerves at a skin temperature of 33–34°C using surface electrodes (Sapphire; Medelec, Woking, U.K.). Quantitative sensory testing was evaluated by VPT at the second metacarpal bone and medial malleolus using the method of limits (Vibrameter; Somedic, Stockholm, Sweden) and by TPTs including warm and cold thresholds at the thenar eminence and dorsum of the foot using the method of limits (TSA-2001; Medoc, Ramat Yishai, Israel) as previously described (7,8). Bedside testing included bilateral assessment of VPT on the medial malleolus using the Rydel-Seiffer AB-125 C-64 Hz tuning fork (Barthelmes, Tuttlingen, Germany) as previously described (13,14). Qualitative measurement of cold perception was performed bilaterally on the dorsum of the foot using the TipTherm device (Gesellschaft für neurologische Diagnostik, Düsseldorf, Germany). This pen-like device consists of a plastic cylinder on one end and a metal cylinder on the other end, with a diameter of 14 mm each. Each end is applied in a random order to the skin for 1 s. The person being tested has to decide which of the two touches feels cooler. Each test included three readings on each side. The test was classified as normal if at least two readings were rated correctly. Accordingly, an abnormal test response was defined if at least two responses were incorrect. However, 8.6% of the 160 healthy subjects gave incorrect responses in all three readings per side, suggesting that the specificity of this device on the foot is relatively low. Neurological examination included the Neuropathy Disability Score (NDS) and the Neuropathy Symptom Score (NSS) as proposed by Young et al. (18). Distal symmetric polyneuropathy was diagnosed if two or more of the following criteria were present: *1*) slowing in nerve conduction velocity in at least two out of four nerves, *2*) elevated metacarpal and/or malleolar VPT, *3*) increased warm and/or cold TPT on the foot, *4*) absent ankle reflexes, and *5*) reduced sensation on the foot.

NeuroQuick testing

The NeuroQuick (Schweers, Meerbusch, Germany) is an instrument for quantitative bedside testing of cold thermal perception based on the wind chill factor, i.e., the effect that wind has on the perception of cold. This handheld, easy-to-handle, microprocessor-operated electronic device has outline dimensions of 135 × 58 × 25 mm (5.31 × 2.28 × 0.98 inches) and a weight of 126 g and is operated by two standard-type Mignon AA (LR6) batteries. The operating temperatures are in the range of −10 to 50°C (14–122°F). The device comprises a fan adjustable to rotate at 10 different velocities (levels), while a constant distance to the skin (23 cm) is ensured by laser diodes. It is based on an ATMEGA8 Processor 2 (Atmel, San Jose, CA) incorporated Class I (0.5mW) Laser at a 635-nm wavelength point to the target at 15.5 cm (6.10 in) distance. The flash ROM embedded application controls a fan (Papst, Landshut, Germany) at revolutions from 1300 to 4600 rpm blowing the accelerated air to the spot at 10 different levels. Hereby, fan revolutions are measured and adjusted to ensure the validated air speed.

The patient is tested in the sitting position on the dorsum of the foot in a quiet ambience in absence of any airstreams in the room. The NeuroQuick is switched on and the patient is given an example to perceive an air flow or cold sensation by holding the device close to the palmar skin at a suprathreshold stimulus. Keeping the eyes closed, the subject is instructed to say "yes" if the air flow is perceived on the skin. The NeuroQuick is set to level 1, and while it is moved slowly toward the skin, the three laser beams produced by the device converge to overlap at one point on the skin at a distance of 23 cm from the dorsum of the foot. This overlap is maintained throughout each test. The assessment starts at level 1, i.e., the lowest velocity of the fan, which is maintained for 5–10 s. If the patient does not perceive the stimulus at this level, level 2 (the next higher fan velocity) is applied for another 5–10 s, etc., until the level at which the air flow is perceived for the first time (threshold) is reached. This sequence is repeated two times. The maximum perceivable level is 10. If the stimulus is not perceived at this level, the threshold is set at level 11. The NeuroQuick threshold (NQT) is defined as the mean of the three readings.

Retinopathy assessment

Color retinal photographs were taken after pupillary dilation using a CR3–45NM nonmydriatic retinal camera (Canon, To-

Table 1—*Clinical data of the control and diabetic subjects*

	Control	DSP$^-$	DSP$^+$
n	160	60	128
Age (years)	45.5 ± 19.4	48.7 ± 13.6	58.0 ± 13.1*
BMI (kg/m^2)	24.7 ± 4.9	28.2 ± 7.5†	28.9 ± 6.1†
Sex (% M/F)	37.5/62.5	56.7/43.3†	60.2/39.8†
Smokers (%)	23.7	20.0	24.2
Room temperature (°C)	22.4 ± 1.5	23.3 ± 1.9†	23.2 ± 2.0†
Type 1/type 2 diabetes (%)	—	45.0/55.0	35.2/64.8
Insulin treatment (%)	—	66.6	80.5‡
Duration of diabetes (years)	—	10.4 ± 10.6	14.7 ± 11.4‡
HbA_{1c} (%)	—	8.7 ± 2.3	9.1 ± 2.0
Triglycerides (mg/dl)	—	127 (39–489)	131 (37–1,660)
Cholesterol (mg/dl)	—	202 ± 49.7	203 ± 42.8
HDL cholesterol (mg/dl)	—	52.0 ± 20.4	48.7 ± 17.5
LDL cholesterol (mg/dl)	—	121 ± 35	119 ± 33.6
Creatinine (mg/dl)	—	0.8 ± 0.2	0.9 ± 0.6
Albuminuria (μg/min)	—	4.8 (0.2–1,737)	8.2 (0.2–3,198)
Retinopathy (%)	—	26.3	46.6‡

Data are means ± SD, median (range), or percent. *$P < 0.05$ vs. control and DSP$^-$; †$P < 0.05$ vs. control; ‡$P < 0.05$ vs. DSP$^-$.

kyo, Japan) and were judged by an experienced examiner.

Nephropathy assessment

Urinary albumin excretion rate was determined from 12-h overnight samples collected on 3 consecutive days using the immuno-nephelometric technique (Array Protein System; Beckman, Fullerton, CA). Diabetic nephropathy was defined as a median urinary albumin excretion rate ≥20 μg/min computed from the three samples.

HbA_{1c} was measured using the high-performance liquid chromatography technique (Diamat; Bio-Rad, Munich, Germany) (normal range 4.2–6.2%).

Statistical analysis

Continuous data were expressed by the arithmetical mean ± SD. Differences between groups were analyzed using the *t* test for two independent samples or the Mann-Whitney *U* test. Qualitative data were analyzed by the Fisher's exact test. Linear regression analysis was used to study associations between variables. Intra-subject day-to-day reproducibility was expressed by the coefficient of variation (CV) and intraclass correlation coefficient using the two-way random effect model and ANOVA, in which the residual mean square corresponds to the within-subject variance. CV was computed from the following equation: $CV = \sqrt{\zeta_w}/\text{mean} \times 100 = SD/\text{mean} \times 100$. The area under the curve with asymptotic 95% CIs were computed for the receiver-operating characteristic curves of the individual nerve function tests based on the aforementioned definition of DSP. The level of significance was set at $\alpha = 0.05$.

RESULTS — In the group of healthy subjects, a significant correlation was noted between NQT and age ($n = 160$, $r = 0.24$, $P = 0.002$). The corresponding equation for NQT was $y = 0.00779 \times (\text{age}) + 0.888$. To obtain a conservative estimate of abnormality, the upper limit of normal was defined at 3 SD above the regression line (99th percentile): $y = 0.00779 \times (\text{age}) + 2.7219$. The CV for the day-to-day reproducibility of NQT in the control subjects ($n = 41$) was 20.4%, while the intraclass correlation coefficient (95% CI) was 0.75 (0.57–0.86). In the diabetic patients ($n = 41$), the CV was 8.5%, while the intraclass correlation coefficient (95% CI) was 0.98 (0.96–0.99).

According to the aforementioned definitions, DSP was excluded in 60 diabetic patients (DSP$^-$), whereas 128 patients had evidence of polyneuropathy (DSP$^+$). The demographic, clinical, and laboratory data of the diabetic groups and healthy control subjects ($n = 160$) are shown in Table 1. The DSP$^+$ group was significantly older than the DSP$^-$ group and the control subjects ($P < 0.05$). BMI and room temperature was significantly higher in the DSP$^-$ and DSP$^+$ groups compared with the control subjects ($P < 0.05$). In the diabetic groups, a higher rate of men was noted compared with the control subjects ($P < 0.05$). No significant differences between the groups were noted for the rates of smokers. The percentage of patients receiving insulin treatment, duration of diabetes, and the rate of retinopathy were significantly higher in the DSP$^+$ group than in the DSP$^-$ group ($P < 0.05$). HbA_{1c}, triglycerides, cholesterol, HDL and LDL cholesterol, creatinine, and albuminuria levels were similar in the diabetic groups studied.

NQT was 1.25 ± 0.63 in the control subjects, 3.09 ± 1.87 in the group without DSP, and 5.68 ± 3.03 in the group with DSP ($P < 0.05$ for DSP$^+$ vs. DSP$^-$, DSP$^+$ vs. control, and DSP$^-$ vs. control). The correlation coefficients of the associations between NQT and the peripheral nerve function tests are shown in Table 2. In both the lower limbs and upper limbs, each of these correlations was significant (all $P < 0.05$). The highest correlation coefficients were noted in the lower limbs for the warm TPT as well as cold TPT and the lowest correlation coefficients were observed for VPT, whereas peroneal MNCV and sural SNCV showed intermediate values. In the upper limbs, the correlation coefficients were lower, with values around 0.2 for the five parameters studied.

The areas under the curve with asymptotic 95% CIs for the receiver-operating characteristic curves of the individual nerve function tests were 0.764 (0.688–0.840) for the Neuro-Quick, 0.603 (0.512–0.694) for the TipTherm, 0.750 (0.672–0.827) for the tuning fork, 0.866 (0.813–0.920) for malleolar VPT, 0.847 (0.789–0.905) for peroneal MNCV, 0.897 (0.852–0.942) for sural SNCV, 0.738 (0.664–0.812) foot warm TPT, and 0.795 (0.727–0.864) for foot cold TPT.

The number and percentages of normal or abnormal nerve function tests in the lower limbs according to normal or abnormal NQT (+3 SD above the age-dependent limit of normal) in the diabetic group with polyneuropathy are shown in Table 3. The combination of abnormal NQT and normal foot warm TPT was significantly more frequent than the opposite, i.e., normal NQT and abnormal foot

Table 2—*Correlations between NQT and the peripheral nerve function tests in the diabetic patients studied*

	r	*n*	*P*
Lower limbs			
Warm perception threshold (Medoc TSA)	0.618	185	<0.001
Cold perception threshold (Medoc TSA)	0.529	184	<0.001
Peroneal MNCV	−0.410	179	<0.001
Sural SNCV	−0.441	177	<0.001
Malleolar VPT (Vibrameter)	0.308	179	<0.001
Malleolar VPT (tuning fork)	−0.358	157	<0.001
Upper limbs			
Warm perception threshold (Medoc TSA)	0.259	185	<0.001
Cold perception threshold (Medoc TSA)	0.188	185	0.010
Median MNCV	−0.203	179	0.006
Median SNCV	−0.220	176	0.003
Metacarpal VPT (Vibrameter)	0.187	180	0.012

warm TPT ($P < 0.05$). Similar significant differences were noted for the constellations with foot cold TPT, TipTherm, and the tuning fork (all $P < 0.05$). In contrast, no significant differences were observed for the comparisons with malleolar VPT (Vibrameter), peroneal MNCV, and sural SNCV. In the diabetic group without polyneuropathy, NQT was abnormal in 26 of 60 patients (43.3%), whereas TipTherm was abnormal in 5 of 59 patients (8.5%) ($P < 0.05$).

CONCLUSIONS — The results of this study demonstrate that the NeuroQuick is a valid and reliable screening instrument for quantitative detection of early small nerve fiber dysfunction in diabetic patients. Because the thresholds determined by the NeuroQuick showed the highest correlations with thermal thresholds as assessed by the Medoc thermal tester, we suggest that small thinly myelinated and unmyelinated nerve fibers are the primary target of the air flow stimulus, although a concomitant mechanical component cannot be entirely excluded. Indeed, a relatively high correlation was also found for VPT and nerve conduction, both of which reflect the integrity of large myelinated nerve fibers.

Perhaps most important is the finding that the NeuroQuick was more sensitive in detecting diabetic polyneuropathy than both elaborate thermal testing as well as the graduated C-64 Hz tuning fork and TipTherm device that were used as screening tests. Indeed, relatively high percentages of patients with DSP ranging from 29 to 47% showed abnormal NQTs, whereas those obtained by the Medoc thermal tester, tuning fork, and TipTherm were normal in these patients. Likewise, a considerable number of patients without DSP had abnormal NQTs. Because we used a conservative cutoff for the upper limit of normal at the 99th percentile (high specificity), we believe that the latter finding may reflect improved sensitivity, i.e., this device could detect neuropathy at an earlier stage than other quantitative tests. These findings have also to be seen in light of the less conservative normal ranges with cutoffs at the 95th percentiles for the other tests. However, there is one caveat in this regard that requires consideration. Although the normative data for the NeuroQuick and TipTherm were obtained from the 160 control subjects described herein, those used for the Medoc system and tuning fork were previously published by others (8,13). Thus, apart from possible methodological bias, it is conceivable that our relatively large control database was more robust than the smaller control samples from the literature. This limitation does not apply to the TipTherm, but the relatively weak performance of this device is not surprising given its merely qualitative and simple algorithm.

The day-to-day reproducibility of the NeuroQuick was very good in healthy subjects and excellent in the diabetic group, suggesting that it is suitable for serial measurements in the routine setting or clinical trials. The intraobserver CV in diabetic patients was 8.5% across the relevant measuring range. This is a considerably lower intra-observer variability compared with that of 41% previously reported for the Semmes-Weinstein monofilament or clinical neurological examination, respectively (19).

The physiology underlying the NeuroQuick method deserves comment. The device is based on the finding that even at low air movement, humans sense a lower temperature than the actual air temperature. This cool-down effect is caused by the wind, humidity, solar radiation, and air and skin temperatures (wind chill effect). Wind chill is the apparent temperature felt on the exposed human body mainly because of the combination of air temperature and wind speed. The wind chill temperature is always lower than the air temperature, even when the air is hotter than the body, because the wind increases the rate at which moisture evaporates from the skin and carries heat away from the body. The

Table 3—*Number of normal or abnormal nerve function tests in the lower limbs according to normal or abnormal NQTs in diabetic patients with polyneuropathy*

	NeuroQuick (+3 SD)		
	Normal	Abnormal	Total
Foot warm TPT			
Normal	26 (21)	42 (34)*	68
Abnormal	6 (5)	51 (41)	57
Total	32	93	125
Foot cold TPT			
Normal	18 (14)	40 (32)*	58
Abnormal	14 (11)	53 (42)	67
Total	32	93	125
Tip Therm			
Normal	29 (23)	58 (47)*	87
Abnormal	3 (2)	34 (27)	37
Total	32	92	124
Tuning fork malleolar			
Normal	15 (14)	31 (29)*	46
Abnormal	11 (10)	50 (47)	61
Total	26	81	107
Malleolar VPT			
Normal	14 (12)	19 (16)	33
Abnormal	16 (13)	70 (59)	86
Total	30	89	119
Peroneal MNCV			
Normal	9 (7)	14 (12)	23
Abnormal	23 (19)	76 (62)	99
Total	32	90	122
Sural SNCV			
Normal	8 (7)	13 (11)	21
Abnormal	23 (19)	77 (64)	100
Total	31	90	121

Data are *n* (%) unless otherwise indicated. *$P < 0.05$.

phase change of water (in sweat) from liquid to vapor requires that the molecules reach a higher energy state. That energy is acquired by absorbing heat from surrounding tissue by conduction (20). The wind chill index and the more widely used wind chill equivalent temperature represent an attempt to combine several weather-related variables into a single index that can indicate human comfort. It has been demonstrated that the wind chill index represents the instantaneous rate of heat loss from bare skin at the moment of exposure to the cold, and as such, it correlates reasonably well with measurable variables that represent a feeling of cold (21). Thus, we believe that the NQT represents primarily an index of small fiber function. In contrast to quantitative thermal testing using Peltier thermode devices that are attached to the skin, this mechanical component is eliminated during the NeuroQuick examination whereby the skin is not being touched.

It is possible that the wind chill effect could be altered in patients with reduced sweat secretion and dryer skin because of a distal sympathetic neuropathy. However, decreased sweat gland activation to cholinergic agents in diabetic patients is not associated with increased thermal perception thresholds. Thus, it has been suggested that diabetic neuropathy has differing effects on afferent and efferent small fibers (22).

The NeuroQuick device uses a simple staircase algorithm to allow for a quick and easy-to-perform screening test in daily clinical practice. We have not used the forced-choice algorithm, which is known to provide accurate and reproducible thermal thresholds yet has some disadvantages: it is time-consuming and the patient's performance may be worsened by reduced attention and boredom (23). Furthermore, it has been suggested that the forced-choice algorithm can be replaced by simpler and quicker ones. In fact, both the forced-choice algorithm and several non–forced-choice algorithms showed a high degree of agreement, and both were suitable for clinical use (23,24). A recent study has shown that the two most widely used devices for cooling detection thresholds (Medoc and CASE IV systems) are interchangeable for research in diabetic polyneuropathy (9). The method-of-limit algorithm of the Medoc device that was used in this validation study is similar to the staircase algorithm of the NeuroQuick. Thus, we are confident that no major disadvantage resulted from not using a forced-choice algorithm.

In conclusion, the NeuroQuick is a valid and reliable screening tool for early and quantitative detection of diabetic polyneuropathy in the daily practice. Because of its high reproducibility and sensitivity, this device could also complement existing tools or scores used in clinical trials evaluating drug effects on diabetic neuropathy.

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