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ORIGINAL COMMUNICATION

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# Quantitative sensory testing and risk factors of diabetic sensory neuropathy

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**Abstract** The goal of this study was to identify risk factors for diabetic peripheral sensory neuropathy in type 2 diabetes mellitus in a Chinese population. Peripheral sensory neuropathy was detected by quantitative sensory testing (5.07/10 g monofilament, neurometer and 128-Hz Riedel Seiffert graduated tuning fork). Those who had two or more abnormal quantitative sensory testings were defined as having diabetic sensory neuropathy. Of the 558 non-insulin dependent diabetes mellitits subjects, 62 (11.1%) had peripheral neuropathy. In 59 (10.6%) detection was by monofilament testing, 45 (8.1%) by graduated tuning fork, and 189 (33.9%) by neurometer. In a multivariate logistic regression model, age and insulin therapy were significantly associated with peripheral neuropathy. Age, serum triglyceride, height, and fasting plasma glucose were independently associated with large fiber neuropathy. Our results confirm the previously identifed multiple risk factors of diabetic neuropathy. Different quantitative sensory testings detect different nerve fiber defects. The weak correlation between these tests indicates the need to use more than one test in screening for diabetic neuropathy.

**Key words** Quantitative sensory testing · Diabetic neuropathy

## Introduction

Peripheral sensory neuropathy is a common complication of diabetes. The Eurodiab IDDM Complications study reported that the prevalence of diabetic neuropathy across Europe was 28%, based on clinical signs and symptoms, vibration perception threshold, tests of autonomic function, and the prevalence of impotence [1]. Neuropathy can predispose the feet to ulceration, gangrenous change, and amputation.

Quantitative sensory testing (QST) was recommended by the consensus conference as a modality for screening of large population [2]. It is a relatively simple, noninvasive, and nonaversive procedure. It can differentiate small versus large fiber deficits and mononeuropathy versus polyneuropathy. It can also detect subclinical neuropathy [3]. It is notable that some patients may have marked neuropathy but be completely asymptomatic. Neurometer is also able to detect neuropathy in the hand [4]. A prospective diabetic foot study conducted in Seattle in the United States found risk factors for peripheral neuropathy to be poor glycemic control, tall height, older age, and alcohol consumption. The actual cause of diabetic neuropathy is not well understood. Metabolic, vascular, and probably genetic factors are thought to be involved [6–8]. Identification of risk factors in a particular patient group is very important so that appropriate treatment can be given for prevention of further deterioration, and preventive measures can be initiated for high-risk patients to prevent foot problems.

We therefore set up a diabetic complication screening clinic to identify the risk factors for complications including diabetic neuropathy and also to identify patients at risk of developing foot ulceration and provide special foot-care education.

## Subjects and methods

A total of 558 type 2 diabetic patients were screened (293 males and 265 females, mean age 61.38 ± 10.01 years, mean duration of diabetes 10.83 ± 7.65 years, mean hemoglobin (Hb) $A_{1c}$ 8.30 ± 1.82%). All were Han Chinese and regularly followed up at diabetic clinic of National Taiwan University Hospital, Taipei, Taiwan. The diagnostic criteria for diabetes mellitus were according to WHO [9].

We obtained information about age, sex, type and duration of diabetes and kinds of treatment. Body mass index (BMI), height, and blood pressure were measured. Laboratory investigations included $HbA_{1c}$, fasting plasma glucose (FPG), serum triglyceride, and total cholesterol. Peripheral vascular disease was detected by vascular Doppler ultrasound using ankle brachial systolic blood pressure index (A-B index). Retinopathy was detected by nonmydriatic color fundus photography. Diabetic nephropathy was defined by the presence of clinical proteinuria and/or elevated blood urea nitrogen/creatinine ratio. Microalbuminuria was defined as urinary albumin concentration of 20–300 mg/l by use of semiquantitative urine dipsticks (Boehringer Mannheim).

QST was performed using the Semmes-Weinstein monofilament test (SWMT), neurometer, and vibration perception test by graduated tuning fork). The Semmes-Weinstein nylon monofilament calibrated to 5.07/10 g (Gillis W. Long, Hansen's Disease Center, Hansen's Disease Foundation, LA, USA) was used to detect pressure sensation. The probe is pressed against the skin until the filament bends. If a person cannot feel the applied pressure at one or more of ten points on either foot, the monofilament test result is defined as positive. Vibration perception was measured with a 128-Hz graduated tuning fork (Riedel Seiffert, Germany). It was applied perpendicularly to the proximal interphalangeal joint of Both big toes. Subjects were requested to respond when they first lost the vibratory sensation. The vibration disappearance threshold was then estimated as the intersection of two virtual triangles that move on the scale from 0 to 8. Average threshold below 4 was defined as positive vibration perception test (VPT). The current perception threshold (CPT) was measured by using a neurometer (Neurotron, Baltimore, MD.). The device emits graded sinusoidal alternating current stimuli at 5, 250, and 2000 Hz at digitally calibrated levels from 0 to 10 mA. Constant current is maintained throughout the stimulation by feedback circuits. The gold electrode was placed on the left big toe and right middle finger. Peroneal (for peroneal nerve) and median (for median nerve) CPT was measured. At each frequency the current was increased over a variable time interval until the subject could perceive a sensation. Then the current was decreased and increased until the subject had any sensation which could be identified as the minimal current intensity. The normal mean median perception thresholds were defined as manufacturer's recommendation: 48 ± 20 for 5 Hz, 84 ± 31 for 250 Hz, and 237 ± 58 for 2000 Hz. The normal mean peroneal perception thresholds were also defined as follows: 78 ± 32 for 5 Hz, 118 ± 37 for 250 Hz, and 323 ± 76 for 2000 Hz. The thresholds above these values for any frequency were deemed to be abnormal.

Univariate and multivariate analyses were performed to examine the differences between neuropathic and nonneuropathic subjects. The $\chi^2$ test was used to compare proportion of dichotomous variables, and Student's *t* test to compare the means of continuous variables. Multivariate analyses using logistic regression were then performed. Variables included in multivariate models were those that differed significantly in the univariate analyses and those suspected as risk factors for neuropathy. Logistic regression analysis was used to analyze the independent effect of significant risk factors on neuropathy. Correlations between individual QSTs were analyzed with nonparametric techniques (Spearman's rank correlation coefficient). A *P* value less than 0.05 was considered to be a significant difference.

## Results

Of the 558 subjects with non-insulin-dependent diabetes mellitus, 59 (10.6%) were positive on SWMT, 45 (8.1%) were positive on VPT, and 189 (33.9%) had abnormal CPT by neurometer examination. Sixty-two (11.1%) who had two or more positive QSTs were defined as peripheral neuropathy according to the Dyck classification [10].

### Peripheral neuropathy

Univariate analysis of factors related to peripheral neuropathy showed that low A-B index (10% vs. 27%, $P < 0.001$), high systolic blood pressure (137.7 vs. 144.6 mm Hg, $P < 0.01$), high FPG (156.1 vs. 171.8 mg/dl, $P < 0.001$), nephropathy including microalbuminuria (9% vs. 15%, $P < 0.01$), and insulin therapy (8% vs. 23%, $P < 0.001$) were associated with neuropathy. Those subjects who had neuropathy were older (60.8 vs. 65.7 years, $P < 0.001$) and had longer duration of diabetes (10.4 vs. 14.1 years, $P < 0.001$). Body mass index, $HbA_{1c}$, height, total cholesterol, serum triglyceride, male sex, and presence of retinopathy had no association with neuropathy although $HbA_{1c}$, and total cholesterol were also higher in those with neuropathy (Table 1).

### Semmes-Weinstein monofilament test

Univariate analysis of factors related to those with positive SWMT revealed that $HbA_{1c}$, systolic blood pressure,

**Table 1** Clinical variables related to neuropathy

| | Neuropathy absent ($n$ = 488) | Neuropathy present ($n$ = 62) | $P^a$ |
|---|---|---|---|
| FPG (mg/dl) | 156.1 ± 2.2 | 171.8 ± 8.2 | 0.027 |
| Age (years) | 60.8 ± 0.4 | 65.7 ± 1.3 | 0.000 |
| BMI (kg/m$^2$) | 24.4 ± 0.1 | 24.5 ± 0.4 | NS |
| Duration (years) | 10.4 ± 0.3 | 14.1 ± 1.0 | 0.000 |
| $HbA_{1c}$ (%) | 8.2 ± 0.0 | 8.6 ± 0.2 | NS |
| Height (cm) | 160.0 ± 0.3 | 160.9 ± 1.0 | NS |
| Systolic blood pressure (mmHg) | 137.7 ± 0.9 | 144.6 ± 2.8 | 0.016 |
| Total cholesterol (mg/dl) | 201.3 ± 1.7 | 209.4 ± 5.2 | NS |
| Triglyceride (mg/dl) | 159.4 ± 4.9 | 185.0 ± 14.8 | NS |
| Low A-B index (%) | 10 | 27 | 0.003 |
| Nephropathy (%) | 9 | 15 | 0.013 |
| Retinopathy (%) | 12 | 10 | NS |
| Male sex (%) | 10 | 12 | NS |
| Insulin treatment (%) | 8 | 23 | 0.000 |

Calculated by Student's *t* test or $\chi^2$ test
NS = not significant

and total cholesterol were higher in these subjects, but the differences were not statistically significant. A higher prevalence of positive SWMT was found in subjects who were older (60.9 vs. 65.3 years, $P < 0.001$), had longer duration of diabetes (10.5 vs. 12.8 years, $P < 0.01$), higher FPG (156.1 vs. 172.7 mg/dl, $P < 0.02$), high triglyceride level (157.3 vs. 203.7 mg/dl, $P < 0.001$), low A-B index (5% vs. 14%, $P < 0.01$) and under insulin treatment (19% vs. 34%, $P < 0.001$). BMI, height, male sex, retinopathy, nephropathy including microalbuminuria were not related to those with positive SWMT.

### Vibration perception test

Univariate analysis of factors related to VPT showed that age (60.8 vs. 67.0 years, $P < 0.001$), duration (10.4 vs. 15.4 years, $P < 0.001$), height (159.8 vs. 163.4 cm, $P < 0.001$) and insulin treatment (7% vs. 14%, $P < 0.01$) were strongly related to those with abnormal VPT. Male sex (6 vs. 10%, $P < 0.05$) and nephropathy including microalbuminuria (6 vs. 11%, $P < 0.05$) were also related to those with positive VPT but the relationship were not strong. None of the other variables mentioned above differed significantly between the two groups with positive or negative VPT.

The above variables were analyzed with multiple logistic regression models. Table 2 shows that overall in the subjects with neuropathy, age and insulin therapy were significantly correlated with peripheral neuropathy. Age, serum triglyceride, and FPG were significantly associated with neuropathy in those with positive SWMT, and age and height in those with positive VPT. Adding nephropathy, including microalbuminuria, to these three models had no significant effect.

**Table 2** Multiple logistic regression analysis of risk factors for diabetic neuropathy

| | Coefficient | Standard error | *P* | Odds ratio |
|---|---|---|---|---|
| Peripheral neuropathy | | | | |
| Age | 0.0343 | 0.0176 | 0.05 | 1.0349 |
| Insulin therapy | 1.1593 | 0.3291 | 0.00 | 3.1878 |
| A-β (large-diameter) fibers neuropathy | | | | |
| Age | 0.0378 | 0.0180 | 0.03 | 1.0386 |
| Triglyceride | 0.0029 | 0.0015 | 0.05 | 1.0029 |
| FPG | 0.0050 | 0.0026 | 0.05 | 1.0050 |
| A-α (large-diameter) fiber neuropathy | | | | |
| Age | 0.0452 | 0.0203 | 0.02 | 1.0462 |
| Height | 0.0898 | 0.0316 | 0.00 | 1.0939 |

Other variables included in the peripheral neuropathy model: A-B index, duration, SBP, sex, total cholesterol, serum triglyceride, height, and FPG. Other variables included in the A-β (large-diameter) fiber neuropathy model: A-B index, duration, SBP, sex, total cholesterol, insulin therapy, and height. Other variables included in the A-α (large-diameter) fiber neuropathy model: A-B index, duration, SBP, sex, total cholesterol, insulin therapy, serum triglyceride, and $HbA_{1c}$

**Table 3** Correlation between QSTs

| | Hand | | Feet | |
|---|---|---|---|---|
| | *r* | *P* | *r* | *P* |
| SWMT/VPT | – | – | 0.30 | 0.00 |
| SWMT/2000 Hz | 0.15 | 0.00 | 0.11 | 0.00 |
| SWMT/250 Hz | 0.17 | 0.00 | 0.11 | 0.00 |
| SWMT/5 Hz | 0.16 | 0.00 | 0.09 | 0.03 |
| VPT/2000 Hz | 0.09 | 0.02 | 0.17 | 0.00 |
| VPT/250 Hz | 0.19 | 0.00 | 0.02 | 0.05 |
| VPT/5 Hz | 0.11 | 0.00 | 0.10 | 0.01 |
| 2000 Hz/250 Hz | 0.40 | 0.00 | 0.51 | 0.00 |
| 250 Hz/5 Hz | 0.52 | 0.00 | 0.66 | 0.00 |
| 2000 Hz/5 Hz | 0.46 | 0.00 | 0.58 | 0.00 |

QSTs = quantitative sensory tests; SWMT = Semmes-Weinstein monofilament test; VPT = vibration perception test

### Correlation between QSTS

The internal correlation between all frequencies of CPT and the correlation between SWMT, VPT, and each CPT frequency are shown in Table 3. A weak but statistically significant correlation was found between SWMT and VPT. The correlation between SWMT, VPT and all three frequencies of CPT are weaker, but internal correlations between CPT frequencies are stronger.

## Discussion

Our choice of 5.07 Semmes-Weinstein nylon monofilament, graduated tuning fork, and neurometer to diagnose peripheral sensory neuropathy was based on several considerations. Donaghue et al. [11] suggested that multiple sites and more than one test should be employed because of the great variability of all QSTs in diabetic subjects. In previous reports all these three tests had been shown to be useful in screening a large population of diabetic neuropathy patients and to identify patients at high risk for lower limb injuries [12–15]. All three QST values can detect both small and large fiber neuropathies. VPT assesses function mainly in Meissner and Pacinian corpuscles, and their associated large diameter fiber (A-α fibers). SWMT assesses the integrity of Merkle touch domes and Meissner corpuscles and their associated large diameter fibers (A-β fibers). By the use of SWMT and VPT we can identify risk factors for large fiber neuropathy. Neurometer has been claimed to be able to test both large and small fibers by using

various frequencies of stimuli. High frequencies CPT (2000 Hz) are significantly correlated with measures of large fiber function, and low frequency CPT (5 Hz and 250 Hz) with small fiber function [16, 17]. In this study the three CPT frequencies were strongly intercorrelated. The correlations of these tests for large fiber function with the three frequencies of neurometer were weak. The weak correlation between 2000 Hz and tests for large fiber function but strong correlation between 2000 Hz and small fiber functions (250 Hz, 5 Hz) suggests that 2000 Hz also has small fiber neuroselectivity.

Body height had been reported as an independent risk factor for neuropathy in persons with diabetes mellitus [5]. Body height serves as a marker for neuronal length and is associated with the absence of distal vibratory perception in patients with diabetes mellitus [18]. Vibratory sensation is strongly related to height, and nerve length should act as a factor in the pathogenesis of diabetic peripheral neuropathy [19]. Taller diabetic men have smaller median and peroneal sensory nerve action potential amplitudes, consistent with a more severe peripheral neuropathy [20]. Our data confirm these reports, and body height can be considered as an uncorrectable risk factor causing diabetic peripheral neuropathy.

Hyperglycemia is a well-established metabolic risk factor of diabetic peripheral neuropathy. Sustained hyperglycemia has been found to be related to functional changes in both peripheral sensory and motor nerve conduction at duration of diabetes of 4 years [6]. The exact mechanisms leading to nerve damage are unknown. The probable mechanisms are sorbital accumulation, myoinositol depletion, and reduced $Na^+$-$K^+$ ATPase activity [7]. Long-term exposure of nerve myelin protein to hyperglycemia may lead to the formation of advanced glycation endproduct and alteration in myelin-macrophage interactions with resulting segmental demyelination [21]. In this study, although FPG was independently associated with neuropathy but not $HbA_{1c}$, the reason may be the cross-sectional design in the study.

Our results confirm the well-established correlation between age and prevalence of neuropathy [1]. Maser et al. [22] reported an acceleration of the natural aging process with regard to nerve function (i.e., large sensory nerve fibers) in diabetes but the mechanism is unclear. Few prior reports have suggested that insulin use is associated with neuropathy in diabetes [23]. In our present analyses insulin therapy itself was indeed an independent factor for diabetic neuropathy in the multiple logistic regression analyses, although the patients' insulin therapy may indicate the severity of the clinical condition. Motor neuropathy has previously been found to be associated with human insulinoma especially following hypoglycemic episodes with a high level of circulating insulin [24]. Experimental studies on insulin administration in diabetic rats show that this results in endoneurial hypoxia, which may cause nerve fiber degeneration [25]. The role of insulin in the development of neuropathy deserves further study.

We were not able to confirm previously associations of neuropathy with low A-B index [5], male sex [26], BMI, duration [27], systolic blood pressure [28], retinopathy, nephropathy and hypercholesterolemia.

In summary, both age and insulin therapy were significantly associated with neuropathy. Age, serum triglyceride, height, FPG, and insulin therapy were independently associated with large fiber neuropathy. Different QSTs can be used to detect different risk factors for different fibers. This is in accord with the multifactorial etiology of diabetic neuropathy. Weak correlations between these tests and various fibers specificities revealed that all these simple, inexpensive tests should be performed in the screening of large populations.

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