

N. Papanas¹
K. Papatheodorou¹
D. Christakidis²
D. Papazoglou¹
G. Giassakis³
H. Piperidou³
C. Monastiriotis¹
E. Maltezos¹

Evaluation of a New Indicator Test for Sudomotor Function (Neuropad[®]) in the Diagnosis of Peripheral Neuropathy in Type 2 Diabetic Patients

Abstract

Sudomotor neuropathy is associated with reduction of plantar sweating and contributes to the pathogenesis of diabetic foot ulcers. The aim of the present study was to evaluate the new indicator test for sudomotor function (Neuropad[®]) in the diagnosis of peripheral neuropathy among type 2 diabetic patients. This study included 104 type 2 diabetic patients (51 men) with a mean age of 64.2 ± 5.6 years and a mean diabetes duration of 12.8 ± 3.7 years. Peripheral neuropathy was diagnosed by means of the Diabetic Neuropathy Index (DNI). Sudomotor neuropathy was assessed by means of colour change in the indicator test. Peripheral neuropathy was diagnosed in 71 patients (68.3%). Sudomotor neuropathy was diagnosed in 67 patients (94.4%) with peripheral neuropathy and in 10 patients (30.3%) without peripheral neuropathy ($p = 0.0001$). Compared with DNI, sensitivity of the indicator test for diagnosing peripheral neuropathy was 94.4% and specificity was 69.7%. Overall prevalence of neurop-

athy was higher using the indicator test (77 patients, 74.0%) than using the DNI (71 patients, 68.3%). Time until complete colour change of the indicator test was 23.8 ± 6.7 min in patients with peripheral neuropathy and 7.7 ± 1.2 min in patients without peripheral neuropathy ($p = 0.001$). Among patients with peripheral neuropathy, time until complete colour change of the indicator test was 14.2 ± 1.9 min in those with a DNI value between 2.5 and 4.5, while it was 32.8 ± 2.6 min in those with a DNI value between 5 and 8 ($p = 0.003$). **Conclusions:** Use of the new indicator test has a very high sensitivity in detection of diabetic peripheral neuropathy. Sudomotor dysfunction can be demonstrated in a considerable part of patients with normal clinical examination. Time until complete colour change of the indicator test is associated with severity of peripheral neuropathy.

Key words

Diabetes mellitus · diabetic peripheral neuropathy · diabetic foot · sudomotor dysfunction

Introduction

Peripheral neuropathy is one of the most common chronic complications of diabetes mellitus and leads to considerable increase in morbidity (La Cava, 2002; Perkins and Bril, 2003; Petit and Upender, 2003; Pittenger and Vinik, 2003; Podwall and Gooch, 2004; Duby et al., 2004). It is of crucial importance in the patho-

genesis of foot ulcers (Litzelman et al., 1997; Boulton et al., 1998; Jude and Boulton, 1999; Mason et al., 1999; Reiber et al., 1999). A neglected component of peripheral neuropathy is sudomotor neuropathy, which results in reduced sweating and dry, sensitive skin with a propensity towards callus and fissure formation (Reiber et al., 1999; Boulton, 2003).

Affiliation

¹ Second Department of Internal Medicine, Democritus University of Thrace, University Hospital of Alexandroupolis, Dragana, Alexandroupolis, Greece

² Diabetic Department, University Hospital of Alexandroupolis, Dragana, Alexandroupolis, Greece

³ Department of Neurology, Democritus University of Thrace, University Hospital of Alexandroupolis, Dragana, Alexandroupolis, Greece

Correspondence

Dr. N. Papanas · Ethnikis Antistasis 44 · Alexandroupolis 68100 · Greece · T + 30 25 51 08 49 72 · F + 30 69 77 54 43 37 · E-mail: papanasnikos@yahoo.gr

Received: May 1, 2004 · **First decision:** June 28, 2004 · **Accepted:** January 8, 2005

Bibliography

Exp Clin Endocrinol Diabetes 2005; 113: 1–4 © J. A. Barth Verlag in Georg Thieme Verlag KG · Stuttgart · New York · DOI 10.1055/s-2005-837735 · ISSN 0947-7349

Numerous tests of sudomotor function have been devised (Reiber et al., 1999; Boulton, 2003). The most important tests include the quantitative sudomotor axon reflex (QSART), the sweat imprint, the thermoregulatory test and the sympathetic skin response (Low, 2003; Vinik et al., 2003). Studies using these tests have shown that sudomotor neuropathy develops early in diabetic patients and can therefore be demonstrated even in asymptomatic patients with normal clinical examination and nerve conduction study (Kennedy and Navarro, 1989; Caccia et al., 1991; Braune and Horter, 1996 ■ Not in references ■; Shimada et al., 2001; Hoeldtke et al., 2001). Nevertheless, these tests are not generally available, because they require expensive equipment and trained personnel (Low, 2003; Vinik et al., 2003).

More recently, a new indicator test (Neuropad®) has been introduced, which measures sweat production on the basis of a colour change from blue to pink (Zick et al., 2003). This new test is an easy-to-perform measure of the sudomotor component of peripheral neuropathy. However, its contribution to the diagnosis of peripheral neuropathy has not been investigated in any other study. Therefore, the aim of the present study was to evaluate this new indicator test in the diagnosis of peripheral neuropathy among type 2 diabetic patients.

Materials and Methods

This study included 104 patients (51 men, 53 women) with type 2 diabetes mellitus. Mean age was 64.2 ± 5.6 years and mean diabetes duration was 12.8 ± 3.7 years. These patients were recruited from the Diabetic Department of the General Hospital of Alexandroupolis, Greece and from the Second Department of Internal Medicine of Democritus University of Thrace, Greece. The control group comprised 20 healthy volunteers (< 40 years old). The study was approved by the institutional ethics committee and all patients gave their informed consent.

Exclusion criteria were peripheral arterial occlusive disease, as well as chronic alcohol abuse, thyroid disease, Vitamin B₁₂ depletion, lumbar spine disorders or any other cause of peripheral neuropathy.

Peripheral neuropathy was diagnosed by means of the Diabetic Neuropathy Index (DNI), as proposed by the University of Michigan (Feldman et al., 1994; Bax et al., 1996). The DNI is a standardized examination of feet appearance (deformity, dry skin, callus, infection and fissures), neuropathic ulceration, Achilles tendon reflexes and vibration perception at great toe using a 128 Hz tuning fork. This examination is applied separately to each foot. Abnormal findings are added to form the DNI score (normal score ≤ 2 , worst score: 8) (Feldman et al., 1994). In the present study patients with a DNI score higher than 2 were considered to have peripheral neuropathy. Peripheral neuropathy was considered moderate in patients with a DNI score between 2.5 and 4.5 and severe in those with a DNI score between 5 and 8.

Sudomotor neuropathy was assessed by means of the new indicator test (Neuropad®) (Zick et al., 2003). Patients were allowed to rest in constant room temperature (25 °C) for 10 min after they had taken off their shoes and socks. Indicator tests were applied

to both soles at the level of the 1st–2nd metatarsal heads and were left until complete colour change from pink to blue. Complete colour change of the test in both feet within 10 min was considered normal response. Patients in whom colour change of the indicator test was completed after 10 min in at least one foot were considered to have sudomotor neuropathy.

Statistical analysis was performed by χ^2 test (using Yates' correction for 2×2 contingency tables) for qualitative variables. Quantitative variables had normal distribution and were compared using *t*-test, ANOVA and least significant difference test. Data were expressed as mean \pm 1 Standard Deviation ($\bar{x} \pm 1$ SD). Statistical significance was defined at a level of 5% ($p < 0.05$).

Results

Peripheral neuropathy was diagnosed in 71 patients (68.3%). Sudomotor neuropathy was diagnosed in 67 patients with peripheral neuropathy (94.4%) and in 10 patients (30.3%) without peripheral neuropathy ($p = 0.0001$), as shown in Table 1. Compared with DNI, sensitivity of the indicator test for diagnosing peripheral neuropathy was 94.4% and specificity was 69.7%. Overall prevalence of neuropathy was slightly ($p = 0.44$, NS) higher using the indicator test (77 patients, 74.0%) than using the DNI (71 patients, 68.3%).

In all persons examined time until complete colour change of the test in the right sole did not differ from time until complete colour change in the left sole ($p = 0.99$, Table 2). Colour change of the indicator test was completed within 10 min in 19 volunteers (95%). Time until complete colour change of the indicator test in healthy volunteers and in diabetic patients with or without peripheral neuropathy is shown in Fig. 1. Time until complete colour change of the test in patients with moderate vs. severe peripheral neuropathy is shown in Fig. 2.

Discussion

This study evaluated the sudomotor component of peripheral neuropathy in type 2 diabetic patients using the new indicator test (Neuropad®). Peripheral neuropathy was clinically diagnosed by means of DNI (Feldman et al., 1994; Bax et al., 1996).

Table 1 Sudomotor neuropathy in diabetic patients with or without peripheral neuropathy

Patients	With peripheral neuropathy	Without peripheral neuropathy	Statistical evaluation
With sudomotor neuropathy	67 (94.4%)	10 (30.3%)	$p = 0.0001$ ($\chi^2 = 44.8$)*
Without sudomotor neuropathy	4 (5.6%)	23 (69.7%)	$p = 0.0001$ ($\chi^2 = 44.8$)*
Total	71	33	104

* *p* value refers to the difference between patients with peripheral neuropathy and those without peripheral neuropathy

Table 2 Time until complete colour change of the indicator test in right vs. left foot

<i>Time until complete colour change of the test (minutes)</i>			
<i>Persons examined</i>	<i>Right foot</i>	<i>Left foot</i>	<i>Statistical evaluation</i>
Controls	4.6 ± 0.7	4.6 ± 0.6	p = 0.99
Patients without peripheral neuropathy	7.7 ± 1.2	7.6 ± 1.2	p = 0.99
Patients with peripheral neuropathy	23.8 ± 6.7	23.9 ± 6.4	p = 0.98

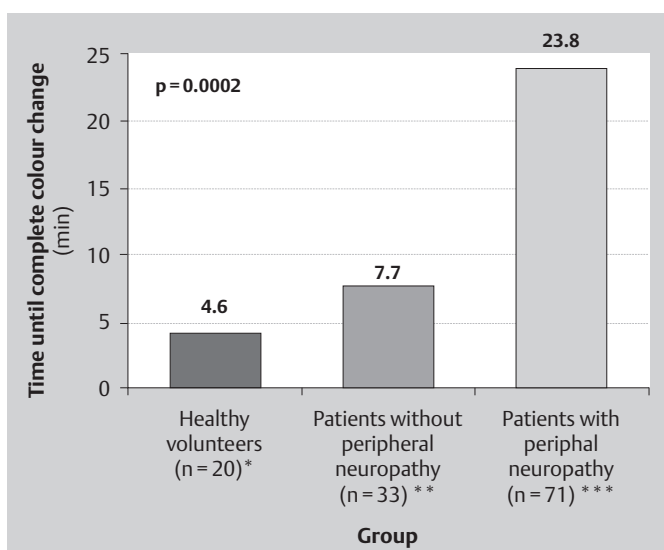


Fig. 1 Time until complete colour change of the test in healthy volunteers (4.6 ± 0.7 min), in diabetic patients without peripheral neuropathy (7.7 ± 1.2 min) and in diabetic patients with peripheral neuropathy (23.8 ± 6.7 min), p = 0.0002. * vs. ** p = 0.033, * vs. *** p = 0.0001, ** vs. *** p = 0.001.

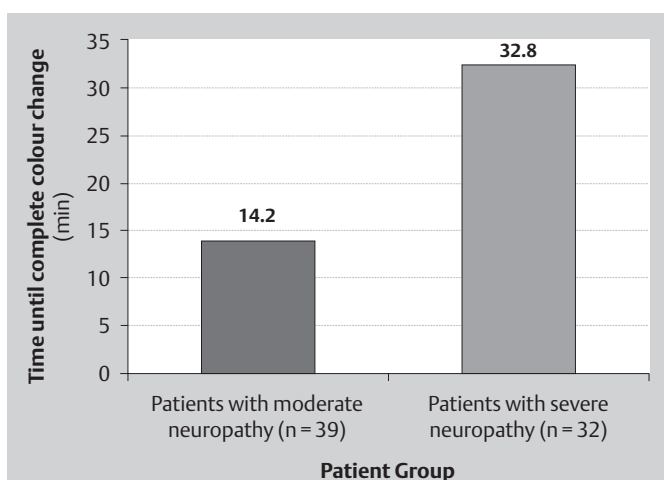


Fig. 2 Time until complete colour change of the test in diabetic patients with moderate (14.2 ± 1.9 min) vs. severe peripheral neuropathy (32.8 ± 2.6 min), p = 0.003.

Frequency of peripheral neuropathy was 68.3%. Prevalence of diabetic peripheral neuropathy is known to differ considerably, according to type of patients studied and diagnostic criteria (Pirart, 1978 a; Pirart, 1978 b; Ziegler et al., 1987; the DCCT Research Group, 1988; Maser et al., 1989; Young et al., 1993; Ahroni et al., 1994; Dyck et al., 1997; Forrest et al., 1997; Fedele et al., 1997; Boulton, 1998). Fedele et al. used the DNI as a screening test in an epidemiological study and reported that 32.3% of patients had neuropathy (Fedele et al., 1997). The higher prevalence of neuropathy in our study as compared to Fedele et al. may be attributed to the fact that we included a smaller number of patients and recruited patients who were attending the Diabetic Department or were hospitalized. Therefore, our results are not representative of the epidemiology of neuropathy in a diabetic population.

Sudomotor neuropathy was diagnosed in 94.4% of patients with peripheral neuropathy and in 30.3% of those without peripheral neuropathy. This difference was highly significant (p = 0.0001). Compared with DNI, sensitivity of the indicator test for diagnosing peripheral neuropathy was 94.4% and specificity was 69.7%. Specificity was only 69.7%, because sudomotor dysfunction was also diagnosed in 30.3% of patients with normal DNI score. This is probably due to the fact that sudomotor dysfunction develops early in the course of diabetes and can be detected even in patients with normal clinical examination and nerve conduction study (Kennedy and Navarro, 1989; Caccia et al., 1991; Braune and Horter, 1996; Shimada et al., 2001; Hoeldtke et al., 2001). Our results are in accordance with those of Zick et al. (2003). However, we used a more homogeneous group of patients, enrolling exclusively type 2 patients. Besides, we employed the standardized and validated DNI score for a more precise diagnosis of peripheral neuropathy.

Prevalence of diabetic neuropathy was insignificantly higher using the indicator test than using the DNI. We therefore believe that the indicator test may prove sensitive in detection of patients at high risk for diabetic foot complications. The fact that the difference in prevalence did not attain statistical significance is perhaps attributable to the small number of patients. Larger prospective studies are needed to investigate the contribution of Neuropad® to detection of high-risk patients and prevention of foot ulcers.

Time until complete colour change of the indicator test differed significantly between diabetic patients with peripheral neuropathy, diabetic patients without peripheral neuropathy and healthy volunteers. Time until complete colour change was significantly higher in diabetic patients with peripheral neuropathy than in those without peripheral neuropathy. It was significantly lower in healthy volunteers than in either group of diabetic patients (with or without peripheral neuropathy). These results are in agreement with the study by Zick et al. (2003).

Furthermore, time until complete colour change in the present study was examined in relation to the DNI score. Analysis showed that time until complete colour change was significantly higher in patients with severe peripheral neuropathy (DNI score between 5 and 8) than in those with moderate peripheral neuropathy (DNI score between 2.5 and 4.5). Consequently, the indica-

tor test was a reliable diagnostic tool not only of the presence but also of the severity of peripheral neuropathy. This result suggests that the indicator test may find a novel use in clinical practice, helping to quantify the reduction of sweat production due to neuropathy and thus – indirectly – the risk for foot ulceration. This is particularly important, since application of the test is easy and interpretation of results does not require patient cooperation. The easy applicability of the test in our study, even in patients of low educational level, was in contrast to vibration perception (as included in the DNI score).

Moreover, time until complete colour change of the test did not differ between the two soles. This association was demonstrated in all persons examined, regardless of the presence of diabetes and regardless of the diagnosis of peripheral neuropathy. Thus, the test showed very good intra-individual reproducibility. This finding offers further evidence that the test is a reliable index of sudomotor function per se and is independent of minor local skin factors which may be different in one foot. Further studies might examine if the test can consistently be applied to one foot only, which is expected to reduce cost and time needed for the procedure.

In conclusion, use of the new indicator test has a very high sensitivity in diagnosis of peripheral neuropathy among type 2 diabetic patients. Sudomotor dysfunction can even be demonstrated in a considerable part of patients with normal clinical examination. Furthermore, time until complete colour change of the test may be used to assess severity of peripheral neuropathy. Therefore, the new indicator test may prove useful in detection of patients at high risk for diabetic foot complications.

References

- Ahroni JH, Boyko EJ, Davignon DR, Pecoraro RE. The health and functional status of veterans with diabetes. *Diabetes Care* 1994; 4: 318–321
- Bax G, Fagherazzi C, Piarulli F, Nicolucci A, Fedele D. Reproducibility of Michigan Neuropathy Screening Instrument (MNSI). *Diabetes Care* 1996; 19: 904–905
- Boulton AJM, Gries FA, Jervell J. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 1998; 15: 508–514
- Boulton AJM. Guidelines for diagnosis and outpatient management of diabetic peripheral neuropathy. *European Association for the Study of Diabetes. Neurodiab Diabetes Metab* 1998; 24: 55–65
- Boulton AJM. The diabetic foot. In: Gries FA, Low PA, Cameron NE, Ziegler D (Eds). *Textbook of Diabetic Neuropathy*. Stuttgart: Georg Thieme Verlag, 2003: 295–305
- Caccia MR, Dezuanni E, Salvaggio A, Osio M, Bevilacqua M, Norbiato G, Mangoni A. Sympathetic skin response versus maximum motor and sensory conduction velocity to detect subclinical neuropathy in non-insulin dependent diabetes. *Acta Neurol Belg* 1991; 91: 213–222
- Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: an intensive review. *Am J Health Syst Pharm* 2004; 61: 160–173
- Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. *Neurology* 1997; 49: 229–239
- Fedele D, Comi G, Coscelli C, Cucinotta D, Feldman EL, Ghirlanda G, Greene DA, Negrin P, Santeusano F and the Italian Diabetic Neuropathy Committee. A multicenter study on the prevalence of diabetic neuropathy in Italy. *Diabetes Care* 1997; 20: 836–843
- Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994; 17: 1281–1289
- Forrest KYZ, Maser RE, Pambianco G, Becker DJ, Orchard TJ. Hypertension as a risk factor for diabetic neuropathy. *Diabetes* 1997; 46: 665–670
- Hoeldtke RD, Bryner KD, Horvath GG, Phares RW, Broy LF, Hobbs GR. Redistribution of sudomotor responses is an early sign of sympathetic dysfunction in type 1 diabetes. *Diabetes* 2001; 50: 436–443
- Jude EB, Boulton AJM. End-stage complications of diabetic neuropathy. *Diabetes Rev* 1999; 7: 395–410
- Kennedy WR, Navarro X. Sympathetic sudomotor function in diabetic neuropathy. *Arch Neurol* 1989; 46: 1182–1186
- La Cava EC. Your nerves. Neuropathy affects more than 50 percent of people with diabetes. Here's what you can do to prevent it. *Diabetes Forecast* 2002; 55: 67–69
- Litzelman DK, Marriott DJ, Vinicor F. Independent physiological predictors of foot lesion in patients with NIDDM. *Diabetes Care* 1997; 20: 1273–1278
- Low PA. Sudomotor function. In: Gries FA, Low PA, Cameron NE, Ziegler D (Eds). *Textbook of Diabetic Neuropathy*. Stuttgart: Georg Thieme Verlag, 2003: 274–278
- Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, Drash AL, Becker DJ, Kuller LH, Greene DA. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes* 1989; 38: 1456–1461
- Mason J, O'Keeffe C, Hutchinson A, McIntosh A, Young R, Booth A. A systematic review of foot ulcer prevention in patients with type 2 diabetes. 1: Prevention. *Diabet Med* 1999; 16: 801–812
- Perkins BA, Bril V. Diabetic neuropathy: a review emphasizing diagnostic methods. *Clin Neurophysiol* 2003; 114: 1167–1175
- Petit WA Jr, Upender RP. Medical evaluation and treatment of diabetic peripheral neuropathy. *Clin Pediatr Med Surg* 2003; 20: 671–688
- Pirart J. Diabetes Mellitus and its degenerative complications: A prospective study of 4400 patients observed between 1947 and 1973. *Diabetes Care* 1978 a; 1: 168–188
- Pirart J. Diabetes Mellitus and its degenerative complications: A prospective study of 4400 patients observed between 1947 and 1973. *Diabetes Care* 1978 b; 1: 252–263
- Pittenger G, Vinik A. Nerve growth factor and diabetic neuropathy. *Exp Diabet Res* 2003; 4: 271–285
- Podwall D, Gooch C. Diabetic neuropathy: clinical features, etiology, and therapy. *Curr Neurol Neurosci Rep* 2004; 4: 55–61
- Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, Boulton AJM. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999; 22: 157–162
- Shimada H, Kihara M, Kosaka S, Ikeda H, Kawabata K, Tsutada T, Miki T. Comparison of SSR and QSART in early diabetic neuropathy: value of length-dependent pattern in QSART. *Auton Neurosci* 2001; 92: 72–75
- The DCCT Research Group. Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). *Diabetes* 1988; 37: 476–481
- Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy: Technical review. *Diabetes Care* 2003; 26: 1553–1579
- Young MJ, Moulton AJM, MacLeod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital population. *Diabetologia* 1993; 36: 150–154
- Zick R, Schäper T, Deeters U. Periphere diabetische Neuropathie. Die Schweißsekretion am Fuß messen. *Kliniker* 2003; 32: 192–194
- Ziegler D, Cicmir I, Wiefels K, Berger H, Gries A. Peripheral and autonomic nerve function in long-term insulin-dependent diabetes. *Diabetes Res* 1987; 4: 9–14