

A Comparison of the New Indicator Test for Sudomotor Function (Neuropad[®]) with the Vibration Perception Threshold and the Clinical Examination in the Diagnosis of Peripheral Neuropathy in Subjects with Type 2 Diabetes

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Key words

- Diabetes mellitus
- diabetic foot
- diabetic neuropathy
- sudomotor function

Abstract

Peripheral neuropathy remains a major cause of morbidity and is a cardinal factor in the pathogenesis of diabetic foot ulceration. The aim of the present study was to compare the new indicator test for sudomotor function (Neuropad[®]) with the vibration perception threshold (VPT) and the clinical examination in the diagnosis of peripheral neuropathy in subjects with type 2 diabetes. This study included 154 type 2 diabetic patients (76 men) with a mean age of 64.3 ± 7.3 years and a mean diabetes duration of 12.8 ± 4.3 years. Neuropathy was diagnosed clinically using the Neuropathy Disability Score (NDS). The VPT was measured with a neurothesiometer, values >25 Volts being classified as abnormal. Sudomotor function was evaluated by the indicator test.

Sensitivity of the indicator test for neuropathy was 97.8% and specificity was 67.2%. Sensitivity and specificity of VPT for neuropathy were 78.9% and 85.9% respectively. A significant correlation was shown between time to colour change of the indicator test and VPT ($r_s=0.889$, $p<0.001$). **Conclusions:** Both the indicator test and the VPT have a high sensitivity for neuropathy. Sensitivity is higher with the indicator test, but specificity is higher with VPT. Time until complete colour change of the indicator test shows a positive correlation with VPT. Thus, the indicator test appears to be a useful additional diagnostic tool of neuropathy, particularly suitable for screening and self-examination, in type 2 diabetes. The correlation between time to colour change of the indicator test and VPT is interesting and merits investigation in a prospective study.

Introduction

Peripheral neuropathy is the most frequent neurologic complication of diabetes (Boulton et al., 2005). While its pathophysiology is complicated (Boulton et al., 2005; Haslbeck et al., 2005; Papanas et al., 2007c), in clinical practice it is associated with increased morbidity and substantially higher risk of foot ulceration (Veves et al., 1993; Boulton et al., 2004; Edmonds, 2004). Clinical examination is the mainstay of diagnosis in everyday practice (Young et al., 1993; Boulton et al., 2004; Boulton et al., 2005). Furthermore, clinical examination is very reliable in estimating the risk for foot ulceration (Kumar et al., 1991; Rith-Najarian et al., 1992; Armstrong et al., 1998; Paisley et al., 2002), as well as in the prediction of wound healing (Zimny et al., 2005). Simple bedside tests, such as the monofilament and the Vibration Perception Threshold (VPT) have proven extremely useful in estimating the risk for foot ulceration (Kumar et al., 1991; Young

et al., 1994; Abbott et al., 1998; Armstrong et al., 1998; Paisley et al., 2002). In particular, a high VPT (VPT >25 Volts) is a significant independent predictor of foot ulceration in prospective studies (Young et al., 1994; Abbott et al., 1998). More recently, the new indicator test for sudomotor function (Neuropad[®]) has become available. A high sensitivity of this test in the diagnosis of neuropathy has been consistently shown (Zick et al., 2003; Manes et al., 2004; Papanas et al., 2005; Marinou et al., 2005; Papanas et al., 2007b). Moreover, results with the indicator test show a significant association with severity of neuropathy, as assessed both by clinical examination (Papanas et al., 2005) and by nerve conduction study (Papanas et al., 2007). Interestingly, an excellent reproducibility of the new test has been reported (Papanas et al., 2005b). However, the indicator test has not been studied in comparison to the VPT. Thus, the aim of the present study was to compare the new indicator test for sudomotor function (Neuropad[®]) with the VPT and

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Table 1 Sudomotor dysfunction, VPT and neuropathy status (presence or absence of neuropathy) in the study population

Sudomotor dysfunction according to neuropathy status			
patients	with neuropathy	without neuropathy	statistical evaluation *
with sudomotor dysfunction	88 (97.8%)	21 (32.8%)	$p < 0.001$
without sudomotor dysfunction	2 (2.2%)	43 (67.2%)	
total	90	64	154
Sudomotor dysfunction according to VPT			
patients	VPT > 25 Volts	VPT \leq 25 Volts	statistical evaluation **
with sudomotor dysfunction	79 (98.8%)	30 (40.5%)	$p < 0.001$
without sudomotor dysfunction	1 (1.2%)	44 (59.5%)	
total	80	74	154
VPT according to neuropathy status			
patients	with neuropathy	without neuropathy	statistical evaluation ***
VPT > 25 Volts	71 (78.9%)	9 (14.1%)	$p < 0.001$
VPT \leq 25 Volts	19 (21.1%)	55 (85.9%)	
total	90	64	154

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

** p value refers to the difference between patients with VPT > 25 Volts and those with VPT \leq 25 Volts

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

with the clinical examination (using the standardised Neuropathy Disability Score as golden standard) in the diagnosis of peripheral neuropathy in subjects with type 2 diabetes.

Patients and Methods

This study included 154 type 2 diabetic patients (76 men, 78 women) with a mean age of 64.3 ± 7.3 years and a mean diabetes duration of 12.8 ± 4.3 years. Patients were recruited from the Second Department of Internal Medicine at Democritus University of Thrace, Greece, as well as from the diabetic department of Alexandroupolis University Hospital, Greece. The study was conducted in accordance with the Helsinki Declaration of Human Rights and all patients gave their informed consent. Recruitment was consecutive and performed in a tertiary care setting.

Exclusion criteria were as follows: age < 17 or > 75 years, peripheral arterial disease, allergy to metals, skin diseases (neurodermatitis, psoriasis, scleroderma, Raynaud syndrome, hyperhidrosis, acrocyanosis), drugs (corticosteroids, antihistaminic and psychoactive drugs, which may affect sweating), chronic alcohol abuse, thyroid disease, Vitamin B₁₂ depletion, lumbar spine disorders or any other cause of peripheral neuropathy.

Neuropathy was diagnosed clinically using the Neuropathy Disability Score (NDS) (Young et al., 1993). This is a standardised examination comprising ankle reflexes, as well as 128 Hz tuning fork, temperature discrimination (hot vs. cold) and pinprick sensation at the hallux, as previously described (Young et al., 1993). Sensory modalities (tuning fork, temperature and pinprick sensation) were scored as 0 = present and 1 = absent on each side, while ankle reflexes were scored as 0 = present, 1 = present with

reinforcement and 2 = absent on each side (Young et al., 1993). Neuropathy was defined as NDS 6 (Young et al., 1993; Paisley et al., 2002)

The VPT was measured with a neurothesiometer (Horwell Scientific Laboratory Supplies, London, UK) whose tractor was applied vertically on the pulp of the hallux. The test was repeated three times and the mean voltage was recorded (Young et al., 1994). VPT was stratified as abnormal (VPT > 25 Volts), intermediate (VPT 15–25 Volts) and normal (VPT < 15 Volts) (Young et al., 1994).

Sudomotor function was evaluated by the indicator test, applied on the plantar aspect of the feet. Time until complete colour change of the test from blue to pink was measured with exactitude of 10 seconds (Papanas et al., 2005; Papanas et al., 2007). Sudomotor impairment was diagnosed in patients with time until complete colour change exceeding 600 seconds in at least one foot (Zick et al., 2003; Papanas et al., 2005; Papanas et al., 2007).

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) 11.0. Significance was assessed by chi-square test (with Yates' correction for 2x2 contingency tables) for qualitative variables. Normally distributed quantitative variables were analysed by t-test and ANOVA. The correlation between time until complete colour change of the test and measures of neuropathy (VPT, NDS) was evaluated by Spearman's correlation coefficient. Data were expressed as mean \pm SD. Significance was defined at the 5% level ($p < 0.05$).

Results

Neuropathy was diagnosed in 90 patients (58.4%). Sudomotor impairment was diagnosed in 88 patients (97.8%) with neuropathy and in 21 patients (32.8%) without neuropathy ($p < 0.001$) (Table 1). Sensitivity of the indicator test for diagnosing neuropathy was 97.8% and specificity was 67.2%, while positive and negative prognostic values were 80.7% and 95.6% respectively. Abnormal VPT was detected in 71 patients with neuropathy and 9 patients without neuropathy ($p < 0.001$) (Table 1). Sensitivity, specificity and positive and negative prognostic values of VPT were 78.9%, 85.9%, 88.8% and 74.3% respectively.

Time until complete colour change of the indicator test was 1308 ± 360 seconds in patients with neuropathy and 544 ± 216 seconds in patients without neuropathy ($p < 0.001$). Time until complete colour change also differed significantly ($p < 0.001$) between patients with high VPT (1680 ± 280 seconds), those with intermediate VPT (930 ± 144 seconds) and those with normal VPT (390 ± 78 seconds). Time until complete colour change of the indicator test (in seconds) showed a significant positive correlation with VPT (in Volts) (Spearman's rank coefficient $r_s = 0.889$, $p < 0.001$) and with NDS (Spearman's rank coefficient $r_s = 0.781$, $p < 0.001$).

Interestingly, sudomotor impairment was diagnosed in all but one patient with abnormal VPT (Table 1). Sensitivity, specificity, positive and negative prognostic values of the indicator test for abnormal VPT (> 25 Volts) were 98.8%, 59.5%, 72.5% and 97.8% respectively. Setting the cut-off value of VPT at 15 Volts, sensitivity, specificity, positive and negative prognostic values of the indicator test for increased VPT (abnormal or intermediate) became 99.1%, 100%, 100% and 97.8% respectively.

Discussion

▼ This study compared the new indicator test for sudomotor function (Neuropad®) with the VPT and the clinical examination in the diagnosis of peripheral neuropathy in type 2 diabetes. Using the clinical examination as a gold standard, the indicator test had a very high sensitivity and a modest specificity for neuropathy. This is in agreement with prior studies (Zick et al., 2003; Manes et al., 2004; Papanas et al., 2005; Marinou et al., 2005; Papanas et al., 2007b). The fact that specificity was only modest may be attributed to the diagnosis of sudomotor impairment in about one third of patients with normal clinical examination, in line with previous findings (Zick et al., 2003; Papanas et al., 2005; Papanas et al., 2007b). This has been explained by the assumption that the indicator test enables the diagnosis of neuropathy at a, possibly, earlier stage when clinical signs are still negative (Papanas et al., 2005; Papanas et al., 2007b). Indeed, there is evidence to suggest that sudomotor dysfunction may, in some patients, be documented early enough, while clinical findings and nerve conduction study are still normal (Braune et al., 1996; Shimada et al., 2001).

Sensitivity and specificity of VPT were 78.9% and 85.9% respectively. In the literature, sensitivity of VPT for neuropathy using the clinical examination as gold standard ranges between 43.66% and 82%, while its specificity ranges between 75% and 94.73% (Davies et al., 1997; Bril and Perkins, 2002; Papanas et al., 2006; Jurado et al., 2007). Arguably, some of this variation may be explained by the differences in patient series (both type 1 and 2 diabetes, young type 1 diabetes only, type 2 diabetes only). Compared with the indicator test, the VPT had a lower sensitivity, but its specificity was considerably higher. The high sensitivity of the indicator test underlines its utility as an emerging screening test.

A significant difference was shown in time until complete colour change of the indicator test between patients with neuropathy and those without neuropathy, in keeping with prior findings (Zick et al., 2003; Papanas et al., 2005). Additionally, in the present study a significant difference in time to colour change was found between patients with high VPT, those with intermediate VPT and those with normal VPT. More interestingly, time until colour change showed a significant positive correlation with NDS. These findings extend the previous observations that time to colour change of the indicator test is associated with severity of neuropathy, assessed both clinically (Papanas et al., 2005) and by nerve conduction study (Papanas et al., 2007).

Furthermore, a significant correlation was shown between time until complete colour change of the indicator test and VPT. One is tempted to consider whether this correlation indicates that measuring the time until colour change of the indicator test might prove an additional surrogate marker of the risk for foot ulceration, given that VPT is a reliable marker of this risk (Young et al., 1994; Abbott et al., 1998). Indeed, for each increment in the VPT by 1 Volt at baseline, the risk of foot ulceration at one year has been found to increase by 5.6% (Abbott et al., 1998). An approximately eightfold relative risk in patients with a VPT > 25 Volts as compared to those with a VPT < 15 Volts has also been reported (Young et al., 1994; Pham et al., 2000). However, the potential contribution of the indicator test to the risk estimation is speculative and can only be confirmed or refuted in prospective studies.

Of further importance, sudomotor impairment was diagnosed in all but one patient with abnormal VPT. Sensitivity of the indica-

tor test for abnormal VPT was very high, while its specificity was modest. Again, the modest specificity is explained by the fact that sudomotor impairment was diagnosed in a considerable part (40.5%) of patients without abnormal VPT. Interestingly, in all patients with sudomotor impairment and VPT 25 Volts, intermediate values of VPT (15–25 Volts) were noted. Thus, setting the cut-off value of VPT at 15 Volts, the indicator test had excellent sensitivity (99.1%) and specificity (100%) for increased VPT (abnormal or intermediate). It may, therefore, be argued that the indicator test has excellent sensitivity and specificity in the detection of patients with high or intermediate risk for foot ulceration, as documented by VPT.

The practical implications of the present study may be summarised as follows. By virtue of its high sensitivity for neuropathy, the indicator test is useful as an additional diagnostic tool of neuropathy in type 2 diabetes. In view of its simplicity, it lends itself particularly to screening and self-examination, while a role in patient education has already been advocated (Papanas et al., 2005; Papanas et al., 2007b). The new correlation between the indicator test and the VPT suggests that the former might also prove of value in the evaluation of the risk for foot ulceration, as has been established for the latter. However, further work is needed to shed light on this issue. It needs to be examined whether the indicator test is accurate in identifying patients with a history of foot ulceration, as it has been shown for the VPT (Vileikyte et al., 1997; Armstrong et al., 1998; Papanas et al., 2006) and the monofilament (Kumar et al., 1991; Rith-Najarian et al., 1992), but also for other tests, like the tactile circumferential discriminator (Vileikyte et al., 1997) or, more recently, the steel ball-bearing test (Papanas et al., 2006). More importantly, prospective studies are needed to investigate whether prolonged time until colour change of the indicator test does, indeed, confer a risk for foot ulceration and, if so, whether this parameter is an independent risk factor.

In conclusion, both the indicator test and the VPT have a high sensitivity for neuropathy. Sensitivity is higher with the indicator test, but specificity is higher with the VPT. Moreover, time until complete colour change of the indicator test shows a positive correlation with VPT. These results suggest a role for the indicator test as an additional diagnostic tool of neuropathy in type 2 diabetes, being particularly suitable for screening, self-examination and education. Its potential contribution to the estimation of the risk for foot ulceration appears interesting and merits investigation in a prospective study.

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