Accuracy of the Neuropad Test for the Diagnosis of Distal Symmetric Polyneuropathy in Type 2 Diabetes

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OBJECTIVE—To estimate the accuracy of Neuropad for the diagnosis and staging of distal symmetric polyneuropathy (DPN) across different stages of neuropathy, using multiple-level likelihood ratios (LRs) to interpret the time necessary to complete the color change of the test.

RESEARCH DESIGN AND METHODS—We conducted a cross-sectional, cohort-type diagnostic accuracy study in 251 consecutive adult type 2 diabetic patients with no peripheral arterial disease or other potential causes of neuropathy, who were recruited between January 2005 and December 2008 from the diabetes outpatient clinics in Alexandroupolis Hospital, Greece. Patients were tested for DPN by means of the neuropathy disability score (NDS) and Neuropad. Multiple-level LRs for time to complete color change were calculated across different stages of neuropathy.

RESULTS—The areas under the curve for the diagnosis of any (NDS of ≥3), at least moderate (NDS of ≥6), or severe (NDS of ≥9) DPN were 0.91, 0.96, and 0.97, respectively. The calculation of multiple-level LRs showed that time to complete color change <360 s suggested the absence of neuropathy. Values between 360 and 1,000 s were indicative of mild neuropathy. Finally, values between 1,000 and 1,200 or >1,200 s were strongly suggestive of moderate or severe DPN, respectively.

CONCLUSIONS—Neuropad could be used as a triage test for the diagnosis and staging of DPN in patients with type 2 diabetes, prompting referral to specialized care setting.

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Distal symmetric polyneuropathy (DPN) is a major debilitating complication of diabetes (1). DPN is associated with a significant increase in morbidity and represents a cardinal etiologic factor for the development of diabetic foot lesions (1–3). Diagnosis of DPN is based on clinical examination to identify neurologic deficits. Clinical practice recommendations of the American Diabetes Association suggest annual screening of patients with diabetes for DPN and advocate diagnosis by means of simple clinical tests, such as the pin-prick sensation, vibration perception (using a 128-Hz tuning fork), or 10-g monofilament pressure sensation (1,4).

Neuropad (Trigocare International, Wiehl, Drabenderhöhe, Germany) is a new diagnostic test with high sensitivity for the diagnosis of DPN (5–9). It is a simple adhesive indicator test that has been found to be suitable for patient self-examination at home (10). Although this holds true for Neuropad interpreted for screening purposes as normal or abnormal after 10 min of application on the plantar aspect of the feet, there is evidence that prolonging the time of observation after application might be useful in increasing the sensitivity for neuropathy and in providing a reliable clue to the severity of neuropathy (6,8). Hence, one might attempt to define multiple-level likelihood ratios (LRs) for Neuropad to increase its diagnostic utility and facilitate prompt specialist referral, where appropriate. The aim of the current study was to examine the accuracy of Neuropad for the diagnosis and staging of DPN across different stages of neuropathy, using multiple-level LRs to interpret the time necessary to complete the color change of the test.

RESEARCH DESIGN AND METHODS

We conducted a cross-sectional, cohort-type diagnostic accuracy study in adult subjects with type 2 diabetes, who were consecutively recruited from the Outpatient Clinic of Obesity, Diabetes, and Metabolism in the Second Department of Internal Medicine, Democritus University of Thrace, Greece, and the Diabetes Clinic, University Hospital of Alexandroupolis, Greece, between January 2005 and December 2008. Individuals meeting any of the following criteria were excluded: age <17 or >75 years, peripheral arterial disease (defined as ankle-brachial index <0.9 in at least one foot, as measured by a Doppler apparatus), other potential causes of neuropathy, thyroid disease, drugs that may affect perspiration, and skin diseases (neurodermatitis, psoriasis, scleroderma, allergy to metals, Raynaud syndrome, hyperhidrosia, or acrocyanosis). The study was conducted and reported in accord with the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) principles (11). The study protocol was approved by an institutional review board, and informed consent was obtained from all subjects.

Characteristics of patients

A total of 340 potentially eligible consecutive adult subjects with type 2 diabetes were identified and informed about the study. Of these, 251 consented to take

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part in the study. Thirty-nine patients were excluded because of exclusion criteria: 30 patients because of peripheral arterial disease, 5 patients because of other causes of neuropathy, and 4 patients because of skin diseases. Finally, 212 patients were included in the study and the analysis (Supplementary Fig. 1). Patient demographics and major clinical characteristics are listed in Table 1. Mean age ± SD of patients was 62 ± 8 years, and 107 (50.5%) patients were men, with a mean duration of diabetes of 11 ± 4 years. All patients underwent both the reference test (neuropathy disability score [NDS]) and Neuropad. Both tests were applied within 2 weeks.

NDS

Distal symmetric polyneuropathy (DPN) was diagnosed through the NDS. The NDS is a standardized examination of ankle reflexes, as well as 128-Hz tuning-fork, pin-prick, and temperature sensation at the hallux (12). It is very reliable, because it encompasses the examination of several modalities and enables a global assessment of neuropathy inasmuch as it permits examination of both large-fiber (ankle reflexes and vibration perception) and small-fiber (pin-prick and temperature sensation) function (12). This contrasts with other diagnostic tests, such as nerve conduction study and skin biopsy, which only examine large- and small-fiber function, respectively (13,14). Of additional significance, NDS has been documented as a reliable strong predictor of the future risk for foot ulceration (1,15). However, the NDS can only be implemented by trained health care professionals and could be criticized for having considerable interobserver disagreement, just like its constituting parts (16).

Based on the NDS score, patients were grouped as having no neuropathy (NDS of 0–2), mild neuropathy (NDS of 3–5), moderate neuropathy (NDS of 6–8), and severe neuropathy (NDS of 9–10) (12,17). The reference test (NDS) was performed by N.P., who was blinded to Neuropad results but might have been aware of patient history and previous HbA_{1c} results.

Neuropad

Examination with Neuropad was performed as previously described (18). Patients were allowed a 10-min acclimatization period in constant room temperature (25°C) after they had removed their socks and shoes. Indicator tests were applied to both soles at the level of the first through second metatarsal heads. The time to color change was defined as the time in seconds that was required until a complete color change of the indicator test from blue into uniform smooth pink and was recorded with exactitude of 10 s. For each patient, we observed the time to color change in each foot and recorded the longer of these two values as more representative of neuropathy status. Examination with Neuropad was carried out by either one of two physicians (D.P. or K.Pap.), blinded to neuropathy status (result of reference test), patient history, and HbA_{1c} results.

Multiple-level LR cutoff points

The choice of multiple-level LR cutoff points is often based on arbitrary criteria. This can be avoided by a priori definition of selection criteria. At the beginning of the study, we decided that we would choose cutoff points based on values deriving from data analysis (receiver operating characteristic [ROC] curves). These would be rounded to numbers that could represent intuitive boundaries. We also decided that we would use the existing cutoff value of 600 s, in order to link our findings with standard clinical practice and make them more clinically relevant (19).

Statistical analysis

Statistical tests were performed using SPSS version 17.0. All values were expressed as means ± SD. Normality was evaluated with the Kolmogorov-Smirnov or the Shapiro-Wilk test, as appropriate. The Mann-Whitney test was used for comparison between two groups, and the Kruskal-Wallis test was used to compare more than two groups. Post hoc multigroup comparison analysis was conducted with the Bonferroni test. The χ^2 test was used for categorical variables. A two-tailed P value of < 0.05 was considered statistically significant. ROC curves were constructed to assess the overall accuracy of Neuropad and to identify optimal cutoffs. The optimal cutoffs of Neuropad were chosen at points with the highest Youden's index (19). Multiple-level LRs were used to explore the relationship between the time to complete color change of the test and neuropathy status. The advantage of this approach is that computation of LRs (unlike sensitivity, specificity, and positive and negative predictive values) does not require dichotomization of test results, which may discard useful diagnostic information. Furthermore, knowledge of the LR of a particular test result enables the calculation of posttest probability for a given patient, using a simple nomogram and the pretest probability (20). CIs of 90% were calculated using CIA software (version 2.1.2; Trevor Bryant, Southampton, U.K.). LRs >10 and <0.1 are considered to provide strong evidence to rule in or rule out diagnoses, respectively (20).

RESULTS—According to the NDS, 4 patients (2%) had no neuropathy (NDS of 0–2), 108 patients (51%) had mild

Table 1—*Characteristics of study participants*

	NDS				
	No neuropathy (0–2)	Mild neuropathy (3–5)	Moderate neuropathy (6–8)	Severe neuropathy (9–10)	*P* (Kruskal-Wallis)
Sex (male/female)	3/1	50/58	33/22	21/24	0.26*
Age (years)	55.2 ± 6.6†	60.2 ± 8.6†	62.2 ± 6.4†	68.3 ± 4.9	<0.001
Diabetes duration (years)	6.0 ± 3.3†‡	9.4 ± 2.8†‡	12.9 ± 2.3†	16.3 ± 4.3	<0.001
HbA_{1c}	7.3 ± 0.3	7.1 ± 0.5	7.1 ± 0.5	7.3 ± 0.6	NS
Neuropad time to color change (s)	402 ± 106†‡	576 ± 197†‡	1,090 ± 295†	1,736 ± 340	<0.001

Data are means ± SD. *χ^2. †$P < 0.008$ vs. NDS = 9–10. ‡$P < 0.008$ vs. NDS = 6–8. A Bonferroni correction was applied and results are reported at a 0.008 level of significance.

neuropathy (NDS of 3–5), 55 patients (26%) had moderate neuropathy (NDS of 6–8), and 45 patients (21%) had severe neuropathy (NDS of 9–10). There was a significant difference in age, diabetes duration, and time to complete color change across groups at different stages of neuropathy ($P < 0.001$) but no such difference in HbA_{1c}.

The diagnostic performance of Neuropad across different stages of neuropathy was assessed by means of the area under the ROC curve. The area under the ROC curve for diagnosis of any distal symmetric polyneuropathy (NDS of ≥3) was 0.91 (90% CI 0.76–1.00). The data-driven optimal cutoff was 365 s, with a sensitivity of 95% (92–97), specificity of 75% (36–94), positive predictive value of 99% (98–100), and negative predictive value of 21% (9–43). The area under the ROC curve for the diagnosis of moderate or severe distal symmetric polyneuropathy (NDS of ≥6) was 0.96 (0.74–0.98). The optimal cutoff was 1,005 s, with a sensitivity of 91% (85–95), specificity of 96% (92–98), positive predictive value of 96% (91–98), and negative predictive value of 92% (87–95). The area under the ROC curve for the diagnosis of severe distal symmetric polyneuropathy (NDS of ≥9) was 0.97 (0.95–0.99). The optimal cutoff was 1,190 s, with a sensitivity of 91% (82–96), specificity of 95% (92–97), positive predictive value of 84% (73–91), and negative predictive value of 98% (95–99) (Table 2).

Multiple-level LRs

The choice of cutoff points was based on predefined criteria. The optimal cutoff points that were calculated from ROC curves for diagnosis of mild, moderate, and severe DPN were 365, 1,005, and 1,190 s, respectively (Fig. 1). These numbers were rounded to the closest ones that could represent an intuitive boundary, in order to facilitate implementation in everyday clinical practice. Hence, we decided to use 360, 1,000, and 1,200 s, adding as a final cut point 600 s, which already is widely used.

Time to complete color change >600 s practically suggested the presence of some kind of neuropathy: the LR for absence of neuropathy (NDS of 0–2) for time to complete color change equal to 600–1,000, 1,001–1,200 or >1,200 is 0.0 (90% CI 0.00–2.39), 0.0 (0.00–2.23), and 0.0 (0.00–2.19), respectively (Table 3). Indeed, a value between 600 and 1,000 was associated with increased probability for mild neuropathy (NDS of 3–5) (7.51 [3.23–18.00]). Time to complete color change between 1,000 and 1,200 was indicative of moderate neuropathy (NDS of 6–8) (12.05 [6.37–23.17]), and values >1,200 s were strongly suggestive of severe neuropathy (NDS of 9–10) (18.44 [9.55–36.35]).

On the contrary, time to complete color change between 360 and 600 s suggested the absence of moderate or severe neuropathy (0.21 [90% CI 0.08–0.51] and 0.00 [0.00–0.22], respectively) and was indicative of mild neuropathy (10.40 [4.54–24.58]). Finally, values <360 s suggested the absence of moderate or severe neuropathy (0.00 [0.00–0.74] and 0.00 [0.00–0.95], respectively) and were suggestive of the absence of any neuropathy (14.18 [4.98–28.12]).

CONCLUSIONS—Neuropad is a new test that already has been shown to yield high sensitivity for the diagnosis of DPN (5–9). The current study is the first to define multiple-level LRs for Neuropad time to complete color change. These now emerge as useful for the detection and staging of DPN. Indeed, we found that any value >600 s excludes all patients without any neuropathy. Specifically, values between 600 and 1,000, 1,000 and 1,200, and >1,200 s are highly suggestive for mild, moderate, and severe neuropathy, respectively. By contrast, time to complete color change <1,000 s practically excludes the possibility of severe clinical neuropathy. Values between 360 and 600 and <360 s are strongly indicative of mild neuropathy and no neuropathy, respectively. Our results verify previous reports suggesting that the dichotomous interpretation of Neuropad (i.e., normal or abnormal at 10 min) discards valuable information (6,8). Conversely, the study of different time thresholds, as shown in this and in previous studies (6,8), although more time consuming, provides additional information on the staged severity of DPN. Taken together, these findings argue for a more detailed interpretation of Neuropad to increase diagnostic information obtained.

The current study has several strengths. The sample represents a large group of consecutive type 2 diabetic patients. Another strength of the study is the methodology: both the indicator and the reference tests were undertaken in all patients, the indicator test was interpreted by two physicians unaware of the results of the reference test or of patients' history and glycemic control, and the results are reported according to STARD principles. A final strength is the practical utility of defining new cutoff values for Neuropad. Use of the latter enhances the diagnostic utility of Neuropad for the diagnosis and staging of DPN and might enable appropriate specialist referral. Therefore, we believe that Neuropad is powerful in the diagnosis and staging of DPN in patients with type 2 diabetes when used in a non-dichotomous approach (by means of multiple-level LRs).

A limitation of this study is the absence of comparison with an alternative diagnostic test, but this was beyond the scope of the present work. An additional limitation is that very few patients had no neuropathy (NDS of 0–2). Complete absence of neuropathic signs was less common in our study than in previous works (17,21). The implication of the very low frequency of no neuropathy could be that the Neuropad cutoff value computed for this category might be less reliable and of diminished external validity for a different population. However, the frequency of no neuropathy and mild neuropathy (i.e., NDS of <6) in the current study was similar to the two previous works. Altogether, it is this threshold of clinically significant neuropathy (NDS of ≥6) that

Table 2—*Accuracy of Neuropad (90% CI)*

	Cutoff (s)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	+LR	−LR
NDS of ≥3	365	95 (92–97)	75 (36–94)	99 (98–100)	21 (9–43)	3.79 (0.91–15.82)	0.07 (0.04–0.14)
NDS of ≥6	1,005	91 (85–95)	96 (92–98)	96 (91–98)	92 (87–95)	25.48 (11.31–57.38)	0.09 (0.06–0.16)
NDS of ≥9	1,190	91 (82–96)	95 (92–97)	84 (73–91)	98 (95–99)	19.02 (10.71–33.78)	0.09 (0.04–0.21)

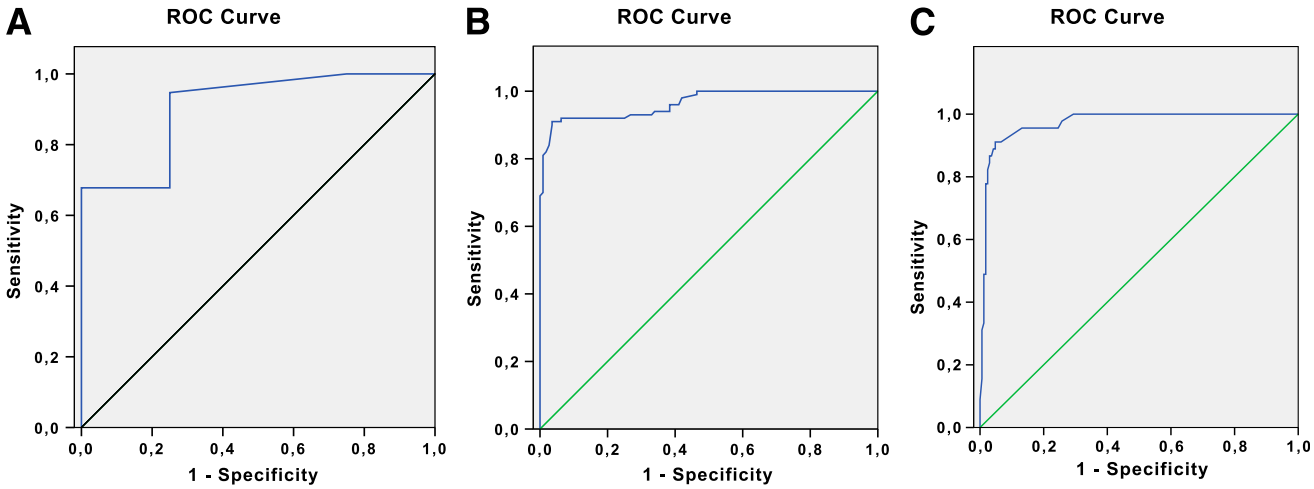

Figure 1—*ROC curves for the diagnosis of any DPN (NDS of ≥3)* (A)*, at least moderate DPN (NDS of ≥6)* (B)*, and severe DPN with Neuropad in the study population* (C)*. The straight line represents diagnosis based on chance alone (area under the curve 0.50). The areas under the ROC curves are as follows: 0.91 (90% CI 0.76–1.00)* (A)*, 0.96 (0.76–0.98)* (B)*, and 0.97 (0.95–0.99)* (C)*. (A high-quality color representation of this figure is available in the online issue.)*

identifies patients at risk for foot ulceration (15). In accordance, the high LR shown for the 1,000-s threshold to detect clinically significant neuropathy underlines the importance of this interpretative approach.

It is important to note that Neuropad does not require involvement of trained health care professionals and is easy to carry out. Therefore, it could be used both by patients and their physicians as a triage test to diagnose clinically relevant neuropathy and prompt referral to specialized care if necessary (22). Moreover, compared with tests proposed in current clinical practice recommendations for general use (4), Neuropad has the incremental advantage of providing some additional information on autonomic neuropathy, as shown by previous studies (7,8). Not to be underestimated, patients with diabetes also may exhibit autonomic neuropathy, which is associated with increased mortality, as recently reaffirmed (23). Thus, Neuropad could be used as an add-on diagnostic test. Finally, Neuropad provides readily visible results, which are comprehensible for the patients themselves. For this reason, it arouses patients' interest in foot care and may be used to promote patient education on diabetic foot complications (5).

The practical implications of the present work could be outlined as follows. In patients with type 2 diabetes, time until complete color change of Neuropad could be measured during their usual medical care. On the basis of this measurement, patients who test negative on the triage test (<360 s) have no DPN or mild DPN, do not need to be examined by the reference test, and require no special medical attention other than general measures of optimal glycemic control, regular foot examination, and education on foot hygiene (4,24,25). At this level, given the reported excellent correlation in Neuropad reading (blue or pink) between physician use and patient self-examination at home (10), it is plausible that Neuropad could be used by the patient himself or herself to rule out any neuropathy. If time to complete color change is not <360 s, the patient should be encouraged to visit a specialist and seek appropriate medical care. Patients with time to color change between 360 and 600 s probably have mild DPN and should be reassessed in a follow-up visit. Likewise, patients with values between 600 and 1,000 s could have mild or moderate DPN and thus need reevaluation with the reference test and monitoring by their treating physicians. Patients with time to color change between 1,000 and 1,200 s have moderate DPN and need more thorough medical attention. They should be referred to a diabetologist and/or podiatrist for initial specialist assessment to determine the necessary frequency of follow-up. Finally, patients scoring >1,200 s appear to have severe DPN and should be promptly referred to the specialized foot care team for evaluation and arrangement of close

Table 3—*Multiple-level LRs (90% CIs) across different stages of neuropathy*

Time to complete color change (s)	NDS			
	0–2	3–5	6–8	9–10
0–360	14.18 (4.98–28.12)	3.46 (1.08–11.33)	0.00 (0.00–0.74)	0.00 (0.00–0.95)
361–600	0.90 (0.16–2.63)	10.40 (4.54–24.58)	0.21 (0.08–0.51)	0.00 (0.00–0.22)
601–1,000	0.00 (0.00–2.39)	7.51 (3.23–18.00)	0.37 (0.15–0.83)	0.00 (0.00–0.30)
1,001–1,200	0.00 (0.00–2.23)	0.09 (0.03–0.23)	12.05 (6.37–23.17)	0.44 (0.19–0.98)
>1,200	0.00 (0.00–2.19)	0.00 (0.00–0.07)	0.57 (0.28–1.09)	18.44 (9.55–36.35)

specialist follow-up (4,24,25). In this simple manner, the indicator test may help toward timely and appropriate identification of high-risk patients.

In conclusion, our results favor the use of Neuropad as a triage test to help toward timely and appropriate identification of high-risk patients. Time to complete color change and multiple-level LRs are of substantial help in the detection and staging of DPN in diabetes. The utility of Neuropad for follow-up of patients with DPN and the optimal frequency that this test should be used remain to be shown. Finally, prospective studies are needed to prove if the results obtained by Neuropad testing predict hard outcomes (mainly foot ulcers).

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N.P. conceived the study, designed the inclusion and exclusion criteria, contributed to data acquisition, wrote the major revision and made comments, had full access to all data, takes responsibility for the integrity of data and the accuracy of data analysis, and had the final decision to submit for publication. P.P. conceived the study, conducted the statistical analysis with guidance from E.M., K.Pal., and A.T., and wrote the first draft of the report. D.P. designed the inclusion and exclusion criteria and contributed to data acquisition. K.Pap. contributed to data acquisition. K.Pal. and E.M. designed the inclusion and exclusion criteria. A.T. conceived the study, wrote the major revision and made comments, had full access to all data, takes responsibility for the integrity of data and the accuracy of data analysis, had the final decision to submit for publication, and is the guarantor. All authors provided important intellectual input and approved the final version of the manuscript.

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References

1. Boulton AJ, Vinik AI, Arezzo JC, et al.; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005;28:956–962
2. Reiber GE, Vileikyte L, Boyko EJ, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care 1999;22:157–162
3. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice: neuropathic diabetic foot ulcers. N Engl J Med 2004;351:48–55
4. American Diabetes Association. Standards of medical care in diabetes: 2010. Diabetes Care 2010;33(Suppl. 1):S11–S61
5. Papanas N, Papatheodorou K, Christakidis D, et al. Evaluation of a new indicator test for sudomotor function (Neuropad) in the diagnosis of peripheral neuropathy in type 2 diabetic patients. Exp Clin Endocrinol Diabetes 2005;113:195–198
6. Papanas N, Giassakis G, Papatheodorou K, et al. Use of the new indicator test (Neuropad) for the assessment of the staged severity of neuropathy in type 2 diabetic patients. Exp Clin Endocrinol Diabetes 2007;115:58–61
7. Liatis S, Marinou K, Tentolouris N, Pagoni S, Katsilambros N. Usefulness of a new indicator test for the diagnosis of peripheral and autonomic neuropathy in patients with diabetes mellitus. Diabet Med 2007;24:1375–1380
8. Spallone V, Morganti R, Siampli M, et al. Neuropad as a diagnostic tool for diabetic autonomic and sensorimotor neuropathy. Diabet Med 2009;26:686–692
9. Kamenov ZA, Petrova JJ, Christov VG. Diagnosis of diabetic neuropathy using simple somatic and a new autonomic (neuropad) tests in the clinical practice. Exp Clin Endocrinol Diabetes 2010;118:226–233
10. Tentolouris N, Achtsidis V, Marinou K, Katsilambros N. Evaluation of the self-administered indicator plaster neuropad for the diagnosis of neuropathy in diabetes. Diabetes Care 2008;31:236–237
11. Bossuyt PM, Reitsma JB, Bruns DE, et al.; Standards for Reporting of Diagnostic Accuracy. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Clin Chem 2003;49:7–18
12. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:150–154
13. Kanji JN, Anglin RE, Hunt DL, Panju A. Does this patient with diabetes have large-fiber peripheral neuropathy? JAMA 2010;303:1526–1532
14. Quattrini C, Jeziorska M, Malik RA. Small fiber neuropathy in diabetes: clinical consequence and assessment. Int J Low Extrem Wounds 2004;3:16–21
15. Abbott CA, Carrington AL, Ashe H, et al.; North-West Diabetes Foot Care Study. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002;19:377–384
16. Stam J, van Crevel H. Reliability of the clinical and electromyographic examination of tendon reflexes. J Neurol 1990;237:427–431
17. Paisley AN, Abbott CA, van Schie CH, Boulton AJ. A comparison of the Neuropen against standard quantitative sensory-threshold measures for assessing peripheral nerve function. Diabet Med 2002;19:400–405
18. Papanas N, Papatheodorou K, Papazoglou D, Monastiriotis C, Christakidis D, Maltezos E. 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. Exp Clin Endocrinol Diabetes 2008;116:135–138
19. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 2006;163:670–675
20. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ 2004;329:168–169
21. Quattrini C, Jeziorska M, Tavakoli M, Begum P, Boulton AJ, Malik RA. The Neuropad test: a visual indicator test for human diabetic neuropathy. Diabetologia 2008;51:1046–1050
22. Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ 2006;332:1089–1092
23. Vinik AI, Maser RE, Ziegler D. Neuropathy: the crystal ball for cardiovascular disease? Diabetes Care 2010;33:1688–1690
24. Lavery LA, Peters EJ, Williams JR, Murdoch DP, Hudson A, Lavery DC; International Working Group on the Diabetic Foot. Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diabetes Care 2008;31:154–156
25. Boulton AJ, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679–1685