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RESEARCH ARTICLE

Evaluation of the Neuropad sudomotor function test as a screening tool for polyneuropathy in the elderly population with diabetes and pre-diabetes: the KORA F4 survey

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Abstract

Background Neuropad is a novel indicator test for sudomotor dysfunction, which has not been validated as a screening tool in a population-based study. This study aimed to evaluate the utility of Neuropad as a screening tool for distal symmetric polyneuropathy among elderly subjects with diabetes and pre-diabetes in the general population.

Methods Eligible subjects aged 61–82 years ($n = 940$) from the KORA F4 survey were examined, 201 of whom had diabetes and 231 had pre-diabetes (WHO 1999 criteria). Polyneuropathy was defined by the Michigan Neuropathy Screening Instrument (MNSI) score >3.

Results Polyneuropathy was diagnosed in 60 (29.9%) subjects with diabetes and in 45 (19.5%) subjects with pre-diabetes, respectively ($p = 0.013$). The sensitivity and negative predictive value of Neuropad (reading time: 10 min) for the diagnosis of polyneuropathy were moderately high, reaching 76.7% and 78.1% in subjects with diabetes and 57.8% and 76.5% in those with pre-diabetes, respectively. Conversely, the specificity and positive predictive value for the diagnosis of polyneuropathy were rather low: 35.5% and 33.6% in diabetic individuals and 33.3% and 17.3% in subjects with pre-diabetes, respectively. Use of the >2 cut-off and MNSI combined with monofilament examination did not improve the diagnostic performance of Neuropad.

Conclusions In the elderly general population with diabetes and pre-diabetes, Neuropad has reasonable sensitivity but rather low specificity for the diagnosis of polyneuropathy. It is a useful simple and inexpensive tool to screen for and to exclude polyneuropathy as desired, while its low specificity implies that a longer reading time merits consideration. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords diabetic polyneuropathy; pre-diabetes; sudomotor dysfunction

Introduction

Distal symmetric polyneuropathy affects approximately one third of the population with diabetes [1], but it may also be encountered in pre-diabetic subjects with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [2–4]. In clinical practice, diagnosis is based on simple clinical tests such as pin-prick sensation, vibration perception (using a 128-Hz tuning fork) or 10-g monofilament pressure sensation [1]. Neuropad is a novel indicator test assessing

sudomotor function on the basis of a colour change from blue to pink [5]. The test has been shown to yield high sensitivity and moderate specificity for polyneuropathy [5–9]. However, the diagnostic performance of Neuropad in earlier works was only examined in patients from diabetes clinics and not in a population setting. To the best of our knowledge, the indicator test has been used for the diagnosis of polyneuropathy neither in subjects with pre-diabetes nor in the elderly population. Thus, the aim of the present study was to assess the utility of Neuropad for the diagnosis of polyneuropathy among elderly subjects with diabetes and pre-diabetes from the general population.

Materials and methods

The present data are based on the KORA (Cooperative Health Research in the Region of Augsburg) F4 Study (2006–2008): this was a follow-up of the KORA S4 study, a population-based health survey conducted between 1999 and 2001. In brief, a total sample of 6640 subjects was drawn in a two-stage cluster sample from the target population consisting of all German residents of the region aged 25 to 74 years. Of the randomly selected 6640 subjects, 4261 (64.2%) participated in the S4 baseline study, 3080 of whom participated in the KORA F4 study (response: 79.6%). The present study focused on 2656 subjects aged 55–74 years from the S4 survey, who were living in the region of Augsburg, Germany, in 1999 [10,11]. Of these, 1653 participated and 1353 had an oral glucose tolerance test (OGTT) at baseline. This cohort was re-examined between 2006 and 2008 (F4 survey) [11]. Included were 1129 subjects, 189 of whom were excluded because of neurological diseases, leaving 940 subjects available for examination. The investigations were carried out in accord with the Declaration of Helsinki and included written informed consent from all participants. All study methods were approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany).

After an overnight fast of at least 10 h, all non-diabetic participants underwent a standard 75-g OGTT [10,11]. Newly diagnosed diabetes, IFG, IGT and normal glucose tolerance (NGT) were defined according to the 1999 World Health Organization diagnostic criteria [12]. Information on sociodemographic variables, lifestyle and risk factors was gathered during a standardized interview. All participants underwent an extensive standardized medical examination, as described in more detail elsewhere [10,11].

Subjects were classified as having diabetes on the basis of self-reported physician diagnosis of diabetes or use of antidiabetic medication. Subjects without diabetes were evaluated by an OGTT. The latter identified subjects with IFG, IGT and newly diagnosed diabetes [12]. Subjects with new diagnosis of diabetes were grouped together with those having known diabetes. Subjects with IFG and IGT comprised the pre-diabetic group. In total, 487 subjects had NGT, 209 had diabetes and 244 had pre-diabetes. The present study assessing the diagnostic utility of Neuropad focused on subjects with diabetes and pre-diabetes. After exclusion of eight subjects with diabetes and 13 subjects with pre-diabetes because of incomplete data on polyneuropathy, 201 subjects with diabetes and 231 with pre-diabetes were available for analysis. The former included 53 subjects with new and 148 subjects with known diabetes. The latter included 45 subjects with IFG, 146 subjects with IGT and 40 subjects with combined IFG/IGT. Of the 487 subjects with NGT, 471 had complete data for analysis.

Polyneuropathy was diagnosed by the Michigan Neuropathy Screening Instrument (MNSI) [13]. This is a standardized and recently validated [14] examination of feet appearance, presence or absence of ulceration, ankle reflexes and vibration perception at the hallux using a graded 128-Hz Reidel-Seiffer tuning fork [13]. Interpretation of tuning fork results was based on age-dependent normal values previously published [15]. A cut-off point of MNSI > 3 was used to obtain maximum specificity and positive predictive value (PPV) for the diagnosis of polyneuropathy [14,16]. We also used the MNSI cut-off 2, according to the original proposal [13].

In addition, patients were examined by using 10 g Semmes Weinstein monofilament (SWMF) (Twin Tip GmbH, Heinsberg, Germany). Examination was performed on the dorsal surface of the distal phalanx of the hallux. The SWMF was pressed against the skin surface until it buckled, and the participant was asked to report whether he or she felt the pressure. Application was repeated ten times on each foot. Normal response was defined as $>8/10$ correct answers and abnormal response as $\leq 8/10$ correct answers [17]. The SWMF was included in the MNSI, which was then called MNSI-MF (MNSI including additional SWMF examination). Two cut-off scores were examined: MNSI-MF > 2 and MNSI-MF > 3. In addition, the diagnostic performance of Neuropad against the SWMF *per se*, defined as abnormal results bilaterally, was examined.

Neuropad® (Trigocare GmbH, Wiehl, Drabenderhöhe, Germany) examination was carried out, as previously described [5], by operators who were blinded to subjects' neuropathy status. The indicator test was applied on a callus-free area between the first and second metatarsal head on the plantar aspect of the foot. The result was read at 10 min (normal = complete colour change from blue to pink; abnormal = no/incomplete colour change) [5].

Statistical analysis was carried out with SPSS 19 (Statistical Package for Social Sciences, Chicago, IL). Normally distributed continuous variables were analysed by *t* test. Qualitative variables were compared by Fisher's exact test. Sensitivity, specificity, PPV, negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR−) and accuracy of Neuropad for the diagnosis of polyneuropathy were calculated by standard formulae against the two cut-off scores of MNSI and MNSI-MF as well as against SWMF. The correlation between Neuropad result and pain score was examined by using Spearman's rank correlation coefficient. The level of significance for two-sided testing was set uniformly at $\alpha = 0.05$.

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Results

The demographic and clinical data of the diabetic and pre-diabetic groups studied are shown in Table 1. Subjects with diabetes had a significantly higher body mass index, waist circumference, triglyceride, uric acid and HbA_{1c} values, as well as fasting and post-load plasma glucose levels and significantly lower cholesterol, LDL cholesterol and HDL cholesterol levels. Paraesthesias and numbness were also significantly more frequent in the diabetic group (all $p < 0.05$). The percentage of regular smokers was significantly higher, and that of physically active subjects was lower in the diabetic group (both $p < 0.05$). No significant differences between the groups were noted for age, sex, systolic and diastolic blood pressure, creatinine levels, alcohol consumption, vibration perception threshold, MNSI, MNSI-MF and pain intensity. One subject with diabetes but none with pre-diabetes had foot ulceration. Two subjects with pre-diabetes and one with diabetes had Charcot neuro-osteoarthropathy.

In subjects with NGT, prevalence of polyneuropathy (MNSI > 3) was 17.2% ($p = 0.104$ *vs*. pre-diabetes, $p < 0.0001$ *vs*. diabetes). The percentages of pre-diabetic and diabetic subjects with polyneuropathy according to the two MNSI scores and cut-offs used are presented in Table 2. In both the diabetic and pre-diabetic groups, the rates of polyneuropathy were highest, when the MNSI-MF score > 2 was used and lowest when the MNSI score 3 was used. While no significant differences in the percentages of polyneuropathy between the groups were noted for the MNSI > 2 and MNSI-MF > 2 definitions, the prevalence of polyneuropathy was significantly higher in the diabetic *versus* pre-diabetic group when using the cut-off >3 for both MNSI and MNSI-MF ($p < 0.05$).

Table 2. Percentages of subjects with polyneuropathy according to the MNSI scores and cut-offs used

	Pre-diabetes	Diabetes	*p*
	n (%)	*n* (%)	value
MNSI > 2	72 (31.2)	74 (36.8)	0.223
MNSI-MF > 2	81 (35.1)	86 (42.8)	0.113
MNSI > 3	45 (19.5)	60 (29.9)	0.013
MNSI-MF > 3	50 (21.6)	69 (34.3)	0.004

MNSI, original Michigan Neuropathy Screening Instrument; MNSI-MF, MNSI including 10 g monofilament.

Abnormal Neuropad results were obtained in 342 subjects (72.6%) with NGT, in 150 subjects with pre-diabetes (64.9%) and in 137 subjects with diabetes (68.2%).

The diagnostic performance of the Neuropad using the different definitions of polyneuropathy in the diabetic and pre-diabetic groups is summarized in Table 3. The sensitivity and NPV of Neuropad for the diagnosis of polyneuropathy were moderately high in subjects with diabetes, ranging from 74.4% to 76.7% and from 65.6% to 78.1%, respectively, and slightly lower in individuals with pre-diabetes, ranging from 57.8% to 68.1% and from 65.4% to 76.5%, respectively. There were no apparent differences in sensitivity and NPV between the various definitions of

Table 1. Demographic and clinical characteristics of the subjects with pre-diabetes and diabetes studied

	Pre-diabetes	Diabetes	*p* value
n	231	201	—
IFG/IGT/IFG + IGT (%)	19.5/63.2/17.3	—	—
New DM/known DM (%)	—	26.4/73.6[a]	—
Age (years)	71.5 ± 5.2	71.8 ± 5.5	0.636
Sex (% male)	53.7	58.2	0.382
BMI (kg/m²)	29.1 ± 4.3	31.1 ± 4.8	<0.001
Waist circumference (cm)	99.2 ± 11.7	104.5 ± 11.8	<0.001
Systolic blood pressure (mmHg)	131 ± 18.9	132 ± 20.5	0.866
Diastolic blood pressure (mmHg)	75.3 ± 10.2	74.0 ± 11.0	0.203
Cholesterol (mg/dL)	223 ± 40.6	206 ± 40.4	<0.001
LDL cholesterol (mg/dL)	142 ± 36.0	127 ± 34.3	<0.001
HDL cholesterol (mg/dL)	54.4 ± 14.0	50.1 ± 11.4	0.001
Triglycerides (mg/dL)	139 ± 67.6	162 ± 124	0.016
Creatinine (mg/dL)	0.96 ± 0.24	0.99 ± 0.25	0.190
Uric acid (mg/dL)	5.7 ± 1.3	6.1 ± 1.5	0.005
HbA_{1c} (%)	5.7 ± 0.3	6.6 ± 0.9	<0.001
Plasma glucose 0 min (mg/dL)	104 ± 11.2	132 ± 34.4	<0.001
Plasma glucose 120 min (mg/dL)	153 ± 25.5	211 ± 36.4	<0.001
Alcohol consumption (g/day)	14.0 ± 16.2	13.5 ± 21.5	0.780
Regular smokers (%)	2.8	7.0	0.046
Physically active (%)	49.8	38.6	0.020
VPT (tuning fork) right great toe	5.6 ± 1.9	5.4 ± 1.7	0.466
VPT (tuning fork) left great toe	5.7 ± 1.7	5.6 ± 1.7	0.424
MNSI (original)	2.2 ± 1.4	2.4 ± 1.5	0.263
MNSI (with monofilament)	2.4 ± 1.6	2.6 ± 1.8	0.132
11-Point pain rating scale	2.3 ± 2.3	2.5 ± 2.5	0.231
Pain (*n*, %)	22 (9.5%)	24 (11.9%)	0.438
Paraesthesias (*n*, %)	18 (7.8%)	29 (14.4%)	0.030
Numbness (*n*, %)	22 (9.5%)	33 (16.4%)	0.042

Data are mean ± SD or %;
MNSI: Michigan Neuropathy Screening Instrument; VPT, vibration perception threshold.
[a]Diabetes duration: 9.1 ± 8.5 years.

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Table 3. Sensitivity, specificity, positive and negative predictive values (PPV, NPV), positive and negative likelihood ratios (LR+, LR−) of Neuropad for the different definitions of polyneuropathy in pre-diabetes and diabetes

	Sensitivity [% (95% CI[a])]	Specificity [% (95% CI[a])]	LR+	LR−	PPV [% (95% CI[a])]	NPV [% (95% CI[a])]	Accuracy [% (95% CI[a])]
Pre-diabetes							
MNSI > 2	68.1 (57.9)	36.5 (30.1)	1.1	0.9	32.7 (26.3)	71.6 (62.2)	46.3 (40.8)
MNSI-MF > 2	65.4 (55.8)	35.3 (28.8)	1.0	1.0	35.3 (28.8)	65.4 (55.8)	45.9 (40.3)
MNSI > 3	57.8 (44.5)	33.3 (27.6)	0.9	1.3	17.3 (12.4)	76.5 (67.5)	38.1 (32.8)
MNSI-MF > 3	58.0 (45.4)	33.1 (27.4)	0.9	1.3	19.3 (14.2)	74.1 (64.9)	38.5 (33.2)
MF	50.0 (26.4)	34.1 (28.8)	0.8	1.5	4.7 (2.2)	91.4 (84.4)	35.1 (29.9)
Diabetes							
MNSI > 2	75.7 (66.1)	36.2 (29.1)	1.2	0.7	40.9 (33.8)	71.9 (61.2)	50.7 (44.7)
MNSI-MF > 2	74.4 (65.5)	36.5 (29.0)	1.2	0.7	46.7 (39.4)	65.6 (54.7)	52.7 (46.7)
MNSI > 3	76.7 (66.0)	35.5 (28.8)	1.2	0.6	33.6 (26.9)	78.1 (67.9)	47.8 (41.8)
MNSI-MF > 3	75.4 (65.4)	35.6 (28.7)	1.2	0.7	38.0 (31.0)	73.4 (62.9)	49.3 (43.2)
MF	75.0 (54.4)	32.6 (26.8)	1.1	0.8	10.9 (6.9)	92.2 (84.3)	36.8 (31.1)

MNSI, Michigan Neuropathy Screening Instrument (original description without 10 g monofilament); MNSI-MF, MNSI including 10 g monofilament.
[a]Lower bound of 95% confidence interval.

polyneuropathy. In contrast, the specificity and PPV for the diagnosis of polyneuropathy were relatively low in the diabetic group, ranging from 35.5% to 36.5% and from 33.6% to 46.7%, respectively, and even lower in the pre-diabetic group, ranging from 33.1% to 36.5% and from 17.3% to 35.3%, respectively. The lowest specificity and PPV were noted in the pre-diabetic group for the >3 MNSI and >3 MNSI-MF cut-offs. The likelihood ratios and accuracy were relatively low for each of the different definitions of polyneuropathy used.

There was no correlation between Neuropad results and presence of symptoms or pain intensity (data not shown).

Discussion

This study is the first to examine the utility of Neuropad for the diagnosis of polyneuropathy in elderly diabetic subjects from the general population. Sensitivity ranged between 74.4% and 76.7%, lower than in prior reports [5–8,18–22], but in the same range as reported by Kamenov *et al*. [23]. Specificity was also lower than previously published [5–8,18,19,21–23], but in the same range as reported by Spallone *et al*. [20]. The lower sensitivity and specificity are attributable to the different patient series. Specifically, we have studied elderly subjects (mean age 71.8 years) from the general population, while previous workers have examined younger patients (mean age ranging between 44.9 and 67.3 years) attending specialized diabetes clinics [5–8,18–23], including young patients with type 1 diabetes [6,19,20,22]. Similarly, accuracy (up to 52.7%) was lower than the 63% reported by Kamenov *et al*. [23].

To the best of our knowledge, this is also the first report on the diagnostic performance of Neuropad in pre-diabetes. There is growing interest in the diagnosis of neuropathy in the early stages of impaired glucose metabolism [24], and this analysis confirms previous population-based observations on the presence of polyneuropathy in a substantial proportion of subjects with pre-diabetes [3,4]. Neuropad exhibited a modestly high sensitivity and a rather low specificity for polyneuropathy in this group. Sensitivity, PPV and accuracy were lower in pre-diabetes than in diabetes, but specificity and NPV were comparable between the two groups.

The major strength of the study is the inclusion of subjects from a representative general population rather than from specialized secondary and tertiary care diabetes clinics. Indeed, previous research has focused on selected patients from such clinics [5–8,18–23]. Nonetheless, such selected groups are not representative of subjects with diabetes as encountered in real-life situations, especially in primary care. Therefore, the diagnostic performance of Neuropad could not be generalized to the actual diabetic population [5–8,18–23]. A further strength is the use of four alternative definitions of polyneuropathy to ensure adequate validity of our findings.

The practical implications of the present study may be outlined as follows. Neuropad can easily be used in population studies as a screening tool for polyneuropathy. This application has been suggested by previous reports [5–8,19,21–23], but had hitherto not been confirmed by a population study. The utility of Neuropad as a screening tool is enhanced by its sufficient sensitivity (high in diabetes, modestly high in pre-diabetes). Specificity is rather low, without an apparent difference between diabetes and pre-diabetes. Interestingly, Spallone *et al*. have shown that prolonging the application time from 10 to 15 min resulted in increased specificity without compromising sensitivity [20]. In contrast, we have recently reported that prolonged application time to 15 and 20 min did not improve the diagnostic performance of the Neuropad in patients within the first year of diabetes diagnosis [25]. Whether prolonged application might be useful in elderly patients merits further consideration.

Of note, Neuropad likelihood ratios for polyneuropathy were not high. In diabetes, the positive likelihood ratio was similar to that reported by Spallone *et al*. [20] in a different series, while the negative likelihood ratio was slightly better. Accordingly, it appears that results obtained with Neuropad would benefit from further confirmation or exclusion of polyneuropathy by established diagnostic modalities.

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In conclusion, Neuropad has a moderately high sensitivity for the diagnosis of polyneuropathy among subjects with diabetes and a modestly high sensitivity for those with pre-diabetes in the elderly general population. Its specificity is rather low, without any difference between diabetes and pre-diabetes. The high sensitivity suggests that it may be used as a screening tool, while its lower specificity implies that results would need confirmation by established diagnostic modalities.

Author contributions

D. Z. researched data, contributed to discussion, wrote, reviewed and edited the manuscript. N. P. researched data, contributed to discussion, wrote, reviewed and edited the manuscript. W. R. researched data, contributed to discussion, reviewed and edited the manuscript. M. H. conducted the field study and reviewed the manuscript. M. S. researched data and reviewed the manuscript. C. M. reviewed and edited the manuscript.

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Conflict of interest

D. Z. and N. P. received honoraria for speaking and consulting activities from Trigocare GmbH, the manufacturer of Neuropad. The company was involved neither in study design nor in data collection.

References

1. Tesfaye S, Boulton AJ, Dyck PJ, *et al*. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; **33**(10): 2285–2293.
2. Hoffman-Snyder C, Smith BE, Ross MA, Hernandez J, Bosch EP. Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. *Arch Neurol* 2006; **63**(8): 1075–1079.
3. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. KORA Study Group. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. *Diabetes Care* 2008; **31**(3): 464–469.
4. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. KORA Study Group. Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. *Pain Med* 2009; **10**(2): 393–400.
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**(4): 195–198.
6. 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**(12): 1375–1380.
7. Papanas N, Papatheodorou K, Papazoglou D, Christakidis D, Monastiriotis C, Maltezos E. The new indicator test (Neuropad): a valuable diagnostic tool for small-fiber impairment in patients with type 2 diabetes. *Diabetes Educ* 2007; **33**(2): 257–264.
8. 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**(2): 135–138.
9. Papanas N, Ziegler D. New diagnostic tests for diabetic distal symmetric polyneuropathy. *J Diabetes Complications* 2011; **25**(1): 44–51.
10. Rathmann W, Haastert B, Icks A, *et al*. High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening. The KORA survey 2000. *Diabetologia* 2003; **46**(2): 182–189.
11. Rathmann W, Strassburger K, Heier M, *et al*. Incidence of Type 2 diabetes in the elderly German population and the effect of clinical and lifestyle risk factors: KORA S4/F4 cohort study. *Diabet Med* 2009; **26**(12): 1212–1219.
12. World Health Organisation. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Report of a WHO consultation. WHO: Geneva, 1999.
13. 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**(11): 1281–1289.
14. Moghtaderi A, Bakhshipour A, Rashidi H. Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. *Clin Neurol Neurosurg* 2006; **108**(5): 477–481.
15. Martina IS, van Koningsveld R, Schmitz PI, van der Meché FG, van Doorn PA. Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group. *J Neurol Neurosurg Psychiatry* 1998; **65**(5): 743–747.
16. Ziegler D, Pritchett YL, Wang F, *et al*. Impact of disease characteristics on the efficacy of duloxetine in diabetic peripheral neuropathic pain. *Diabetes Care* 2007; **30**(3): 664–669.
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**(5): 400–405.
18. Papanas N, Giassakis G, Papatheodorou K, *et al*. Sensitivity and specificity of a new indicator test (Neuropad) for the diagnosis of peripheral neuropathy in type 2 diabetes patients: a comparison with clinical examination and nerve conduction study. *J Diabetes Complications* 2007; **21**(6): 353–358.
19. 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**(6): 1046–1050.
20. Spallone V, Morganti R, Siampli M, *et al*. Neuropad as a diagnostic tool for diabetic1 autonomic and sensorimotor neuropathy. *Diabet Med* 2009; **26**(7): 686–692.
21. Papanas N, Papatheodorou K, Papazoglou D, Kotsiou S, Maltezos E. A prospective study on the use of the indicator test Neuropad(R) for the early diagnosis of

peripheral neuropathy in type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2011; **119**(2): 122–125.
22. Freitas C, Carvalho A, Melo-Rocha G, *et al*. The Neuropad test in the screening of peripheral neuropathy in diabetic patients. *Acta Med Port* 2009; **22**(6): 729–734.
23. 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**(4): 226–233.
24. Papanas N, Vinik AI, Ziegler D. Neuropathy in prediabetes: does the clock start ticking early? *Nat Rev Endocrinol* 2011; **7**(11): 682–690.
25. Ziegler D, Papanas N, Roden M, for the GDC Study Group. Neuropad: evaluation of three cut-off points of sudomotor dysfunction for early detection of polyneuropathy in recently diagnosed diabetes. *Diabet Med* 2011; **28**(11): 1412–1415.