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*The Diabetes Educator* 2007; 33; 257  
DOI: 10.1177/0145721707299661

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# The New Indicator Test (Neuropad®)

## A Valuable Diagnostic Tool for Small-Fiber Impairment in Patients With Type 2 Diabetes

### Purpose

The purpose of this study was to evaluate the new indicator test for sudomotor function (Neuropad®) in the diagnosis of small-fiber impairment in patients with type 2 diabetes.

### Methods

This study included 123 patients with type 2 diabetes (59 men; mean age,  $64.3 \pm 8.6$  years; mean diabetes duration,  $12 \pm 6.1$  years). Sudomotor dysfunction was assessed by means of the new indicator test. Neuropathy was diagnosed by the Neuropathy Disability Score and small-fiber impairment by temperature perception (Tipterm device) and pain perception (Neurotip).

### Results

The frequency of sudomotor dysfunction was significantly ( $P = .001$ ) higher in patients with neuropathy (95%) than in those without neuropathy (30.2%). Sensitivity of the indicator test for neuropathy was 95%, and specificity was 69.8%. Frequency of neuropathy was significantly ( $P = .018$ ) higher with the indicator test (74.8%) than with conventional clinical examination (65.4%). Sudomotor dysfunction was significantly ( $P = .001$ ) more frequent in patients with small-fiber impairment (99%) than in those without small-fiber impairment (21.7%). Sensitivity for small-fiber impairment was 99%, and specificity was 78.3%. There was no difference ( $P = .999$ ) in the frequency of small-fiber

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DOI: 10.1177/0145721707299661



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impairment as diagnosed with the indicator test (80.5%) and with clinical examination (81.3%).

## Conclusions

The indicator test has a very high sensitivity and specificity for small-fiber impairment in patients with type 2 diabetes.

Neuropathy is one of the main chronic diabetes-related complications leading to increased morbidity and susceptibility to foot ulceration.<sup>1-6</sup> Diabetic neuropathy may affect the large myelinated nerve fibers, the small (myelinated and unmyelinated) nerve fibers, or both.<sup>7</sup> To date, scientific interest has mainly focused on large-fiber damage in diabetes, while small-fiber impairment has received less attention.<sup>7,8</sup> Indeed, the most popular part of clinical examination (ankle reflexes and tuning fork) and nerve conduction study may easily assess large-fiber function.<sup>3-5</sup> Conversely, the diagnosis of small-fiber function requires more sophisticated tests.<sup>7-10</sup>

The distinction between types of nerve fibers is based on fiber size and presence or absence of myelin sheath.<sup>7,9,10</sup> All large fibers (with a diameter of 6-12  $\mu\text{m}$ ) have a myelin sheath and mediate ankle reflexes, touch, pressure, vibration, and proprioception. Small fibers are either myelinated (A  $\delta$  fibers with a diameter of 1-5  $\mu\text{m}$ ) or unmyelinated (C fibers with a diameter of 0.2-1.5  $\mu\text{m}$ ).<sup>7,9,10</sup> Small fibers mediate sensation of temperature and pain as well as the spectrum of autonomic functions.<sup>7,9,10</sup> Small-fiber neuropathy (or small-fiber impairment) is a subtype of neuropathy, characterized by impairment of small-fiber function and sparing or minimal involvement of large fibers.<sup>7,9,10</sup>

In diabetes, tests of small-fiber impairment rely on examination of somatic and autonomic functions subserved by these fibers.<sup>7-11</sup> Somatic functions include pain sensation and temperature sensation.<sup>7,10</sup> Pain sensation is examined by means of a pinprick that stimulates C fibers. Qualitative evaluation of temperature sensation is performed by using hot and cold tubes to examine sensation of hot (C) and cold (A  $\delta$ ) fibers, respectively.<sup>7</sup> Quantitative evaluation of temperature sensation relies on the measurement of thermal perception threshold.<sup>7,10</sup>

This is assessed by application of an automatically heated or cooled probe on the patients' skin.<sup>7,10</sup> Computer-assisted, operator-independent systems have been developed, enabling the administration of repeatable thermal stimuli and recording of patients' response.<sup>12</sup> Autonomic functions mainly include cardiac autonomic testing and sweat tests.<sup>7,9,10</sup> Cardiac autonomic testing is conducted by recording heart rate variability and changes in blood pressure in response to simple and well-standardized maneuvers, such as deep breathing or standing up from the supine position.<sup>7,10,13</sup> Normal sweat production, known as sudomotor function, may be evaluated by a number of established tests, notably the quantitative sudomotor axon reflex test, the sweat imprint, the thermoregulatory test, and the sympathetic skin response.<sup>7,10,13-15</sup> Regrettably, these tests are not widely applicable because they require expensive equipment and trained personnel.<sup>13-15</sup> A minimally invasive skin biopsy assessing intraepidermal skin nerve fibers is a more modern technique that enables the evaluation of small-fiber function.<sup>7,16</sup>

More recently, a new indicator test for sudomotor function (Neuropad<sup>®</sup>; miro Verbandstoffe GmbH, Wiehl-Drabenderhöhe, Germany) has been introduced.<sup>17,18</sup> This is an easy-to-use patch that assesses plantar sweat production by means of a color change from blue to pink.<sup>17,18</sup> The indicator test contains the complex salt anhydrous cobalt-II-chloride. In the presence of water, this salt absorbs water molecules, changing its color from blue to pink, the time required for complete color change being negatively related to humidity.<sup>19</sup> The new test has been reported to yield results that show good correlation with severity of peripheral neuropathy.<sup>18</sup> Furthermore, the new test has been reported to have excellent reproducibility.<sup>20</sup>

To date, there is a limited number of studies of the new indicator test focused on the contribution of the indicator test to the diagnosis of large- rather than small-fiber impairment.<sup>17,18,21</sup> However, sweat tests traditionally belong to the modalities evaluating small fibers.<sup>7,9,10</sup> Thus, the aim of the present study was to investigate whether the new indicator test enables the diagnosis of small-fiber impairment in patients with type 2 diabetes.

## Methods

This study included 123 patients with type 2 diabetes (59 men, 64 women; mean age, 64.3  $\pm$  8.6 years; mean diabetes

duration,  $12 \pm 6.1$  years). Subjects were recruited from the Second Department of Internal Medicine at Democritus University of Thrace, Greece, and from the Diabetic Department of the General Hospital of Alexandroupolis, Greece. The study was approved by the Institutional Ethics Committee, and all patients gave informed consent.

Diabetic neuropathy was diagnosed by the Neuropathy Disability Score (NDS).<sup>22</sup> This is a standardized examination of ankle reflexes, as well as 128-Hz tuning fork, pinprick, and temperature sensation at the hallux, as described earlier.<sup>22</sup> Patients with an NDS score  $\geq 6$  were considered to have neuropathy.<sup>22,23</sup>

Small-fiber function was assessed by means of temperature and pain perception. Temperature perception was assessed with the Tiptherm device.<sup>24,25</sup> This is a pen-like device comprising a plastic cylinder on one end and a metal cylinder on the other end, with a diameter of 14 mm each. The Tiptherm device was applied 3 times on the dorsum of each foot. An abnormal test result was defined as at least 2 incorrect responses out of 3 readings on the dorsum of each foot.<sup>24,25</sup> Pain sensation (pinprick) was assessed with a calibrated Neurotip (Owen Mumford, Oxford, UK) attached to a Neuropen (Owen Mumford) device.<sup>23</sup> In a random order, the sharp or blunt edge of the Neurotip was pressed against the plantar aspect of the hallux until the guiding markers of the Neuropen were aligned. Patients were asked to distinguish between the painful and painless stimuli. An abnormal test result was defined as at least 2 incorrect responses out of 3 readings on the hallux of each foot.<sup>23</sup> Small-fiber impairment was defined as abnormal temperature and pain sensation.

Peripheral arterial occlusive disease was evaluated by means of the Ankle-Brachial Index (ABI) measurement with a Doppler apparatus. Peripheral arterial disease was diagnosed in patients with  $ABI < 0.9$ .<sup>26</sup>

Exclusion criteria were as follows: aged  $< 17$  years or  $> 75$  years, peripheral arterial occlusive disease, other potential causes of neuropathy (end-stage renal failure, alcohol abuse, malignancy), drugs (corticosteroids, antihistaminic and psychoactive drugs, which may impede sweating), peripheral nerve lesions (traumatic lesions, plexus paresis, spinal root compression, herpes zoster, polyradiculopathy), thyroid disease, and skin diseases (neurodermatitis, psoriasis, scleroderma, allergy to metals, Raynaud syndrome, hyperhidrosia, acrocyanosis).

Sudomotor dysfunction was assessed by means of the newly introduced indicator test (Neuropad<sup>®</sup>).<sup>17,18</sup> All measurements were performed in constant room temperature

and humidity, with a 10-minute period allowed for patient acclimatization after having taken off shoes and socks. The indicator test was applied between the first and the second metatarsal head on the plantar surface of both feet, a common site of neuropathic ulcers. Time until complete color change from blue to pink was recorded. Sudomotor dysfunction was defined as the time until complete color change exceeding 10 minutes in at least 1 foot.<sup>17,18</sup>

Statistical analysis was performed using the Statistical Package for Social Sciences SPSS version 11.0. Significance was assessed by  $\chi^2$  test (with Yates correction for  $2 \times 2$  contingency tables) and by Fisher exact test where appropriate for qualitative variables. Significance was defined at the 5% level ( $P < .05$ ). Sensitivity was defined as the ratio of true positives/(true positives and false negatives). Specificity was defined as the ratio of true negatives/(true negatives and false positives). Positive prognostic value was defined as the ratio of true positives/(true positives and false positives). Negative prognostic value was defined as the ratio of true negatives/(true negatives and false negatives).

## Results and Clinical Implications

Neuropathy was diagnosed in 80 patients (65.4%). Sudomotor dysfunction was diagnosed in 76 patients (95%) with neuropathy and in 16 patients (30.2%) without neuropathy, with a significant difference at  $P = .001$  (Table 1). Sensitivity for neuropathy was 95%, and specificity was 69.8%. Positive prognostic value was 82.6%, and negative prognostic value was 90.2%. Sensitivity was only 69.8% because sudomotor dysfunction was also diagnosed in a substantial part (30.2%) of patients without neuropathy. Presumably, this may be ascribed to the early development of sudomotor dysfunction in diabetes.<sup>27</sup> Indeed, there is evidence to suggest that sudomotor dysfunction may even be detected in patients with normal clinical findings and nerve conduction study.<sup>28,29</sup> Sudomotor dysfunction has been shown to be mediated by small-fiber injury.<sup>15,30</sup> In this context, it is of interest that pathological studies have also been able to show that small-fiber injury may occur early in diabetic patients with normal clinical or electrophysiological findings<sup>31</sup> or even earlier in patients with impaired glucose tolerance.<sup>32,33</sup>

Frequency of neuropathy was significantly ( $P = .018$ ) higher with the indicator test (92 patients, 74.8%) than

Table 1

Sudomotor Dysfunction in Patients With Diabetes According to Clinical Status (Presence or Absence of Neuropathy and Small-Fiber Impairment)

Sudomotor Dysfunction According to Neuropathy Status					
Patients	With Neuropathy		Without Neuropathy		Statistical Evaluation*
	n	%	n	%	
With sudomotor dysfunction	76	95	16	30.2	$P = .001$
Without sudomotor dysfunction	4	5	37	69.8	
Total (n = 123)	80		53		
Sudomotor Dysfunction According to Status of Small-Fiber Impairment					
Patients	With Small-Fiber Impairment		Without Small-Fiber Impairment		Statistical Evaluation†
	n	%	n	%	
With sudomotor dysfunction	99	99	5	21.7	$P = .001$
Without sudomotor dysfunction	1	1	18	78.3	
Total (n = 123)	100		23		
* $P$ value refers to the difference between patients with neuropathy and those without neuropathy.					
† $P$ value refers to the difference between patients with and those without small-fiber impairment.					

with conventional clinical examination (80 patients, 65.4%). A higher prevalence of neuropathy as diagnosed with Neuropad<sup>®</sup> has been reported previously, but this difference did not attain statistical significance.<sup>17,18</sup> The implication of the findings is that the indicator test might prove to be more sensitive in the detection of patients at risk for diabetic foot ulceration.

Small-fiber dysfunction was diagnosed in 100 patients (81.3%). Sudomotor dysfunction was diagnosed in 99 patients with small-fiber impairment (99%) and in

5 patients without small-fiber impairment (21.7%), with a significant difference at  $P = .001$  (Table 1). Sensitivity was 99%, and specificity was 78.3%. Positive prognostic value was 95.2%, and negative prognostic value was 94.7%. There was no difference ( $P = .999$ ) in frequency of small-fiber impairment as diagnosed with the indicator test (99 patients, 80.5%) and with clinical examination (100 patients, 81.3%). Obviously, sensitivity and specificity, as well as positive and negative predictive values for small-fiber impairment were excellent, higher than for neuropathy diagnosed by clinical examination. Essentially, there was no difference in the diagnosis of small-fiber impairment with the indicator test and with clinical examination. The close correlation between sudomotor dysfunction and small-fiber impairment is not surprising given that impaired sweat production is due to small-fiber dysfunction.<sup>15,30</sup> From a practical point of view, it should be emphasized that this ability of Neuropad<sup>®</sup> to diagnose small-fiber impairment may permit timely detection of neuropathy and so prevent underdiagnosis of this serious complication.<sup>25,31,33</sup>

Interestingly, the reduced color change of Neuropad<sup>®</sup> was an impressive finding for the patients themselves. Patients who took part in the study showed a keen interest

in the diagnosis of neuropathy, in self-examination, and in the use of appropriate footwear. Accordingly, an additional advantage of the indicator test was its ability to promote patient education, which has been recognized as an important aspect in overall foot care.<sup>4,6</sup>

The strengths of the indicator test are as follows. The new test has a high sensitivity for the diagnosis of neuropathy. More important, it has excellent sensitivity and specificity for the diagnosis of small-fiber impairment and hence appears to enable early diagnosis of neuropathy. Moreover,

the test is based on an unequivocal color change, which does not require patient cooperation. It also lends itself to self-examination and promotes patient education. Finally, it is an easily applicable diagnostic tool, which may be used as a screening test by all health care providers (including general practitioners, podiatrists, and diabetes nurses) in primary health care. The weakness of the indicator test is that there are, so far, no prospective studies investigating its utility as a potential marker of the risk for foot ulceration. Such studies are eagerly awaited. It also remains to be determined if there is an association between results obtained with Neuropad<sup>®</sup> and the severity of small-fiber impairment (assessed, for instance, by quantifiable thermal perception threshold), given that such an association of Neuropad<sup>®</sup> has been shown for severity of peripheral neuropathy.<sup>18</sup>

In conclusion, the indicator test is very sensitive for neuropathy, and, more important, it has a very high sensitivity and specificity for small-fiber impairment in particular. Interestingly, it enables detection of sudomotor impairment in a considerable part of patients without clinical evidence of neuropathy. In view of these encouraging results and of its easy applicability as a simple, noninvasive diagnostic tool, it appears that the indicator test may prove useful as a screening test of early nerve fiber injury in the diabetic population.

## Implications for Diabetes Educators

This study has shown that the new indicator test (Neuropad<sup>®</sup>) has an excellent sensitivity and specificity as a screening test for small-fiber impairment, thus facilitating early diagnosis of neuropathy in patients with type 2 diabetes. The indicator test may easily be used by all health care providers (including general practitioners, podiatrists, and diabetes nurses) in primary health care. More important, it may be used by the diabetes educator to illustrate the impaired nerve function to the patient as well as to encourage self-examination, and it has been found to promote patient education about foot care.

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