Screening for “at-risk” feet is the job of all of those caring for people with Diabetes.26

Diagnostic Test for Sudomotor Dysfunction and early detection of Diabetic Foot Syndrome, Diabetic Neuropathy13, 22, 23

Included in Toronto Consensus Panel on Diabetic Neuropathy latest recommendation
Published: Diabetes - Metabolism and Reviews, Diabetes Metab Res Rev 2011; 27:
**neuropad®** is a simple, non-invasive indicator test that has been developed for the assessment of sweating and, hence, autonomic innervation of the diabetic foot.

**Diabetic Neuropathy (Distal Symmetric Polyneuropathy)**

- **Motor Neuropathy**
  - Reduced Muscle Flexibility
  - Foot Deformities
  - Diagnostic Tools: Pressure Stat Tendon Reflexes

- **Sensory Neuropathy**
  - Loss of Protective Sensation
  - Decreased pain Sensation Insensate Foot
  - Diagnostic Tools: Tuning Fork 128 Hz Monofilament 10 g Vibratip Ipswich Touch Test Warm-Cold detection

- **Autonomic Neuropathy**
  - Sudomotor Dysfunction Loss of sweating Dry Skin
  - Calluses Fissures Cracked Skin
  - Diagnostic Tools: neuropad®

**Today neuropad® test is the only simple and low cost medical device which documents sudomotor dysfunction, validated with more than 30 clinical study publications.**
The pathway to foot ulceration:
A combination of risk factors that ultimately results in the pathway to skin breakdown.
Autonomic neuropathy leading to dry skin and callus build up at such sites, and can also be regarded as a component cause.\textsuperscript{26}

Peripheral Vascular Disease
Peripheral vascular disease leads to ischaemia

Small Fibre Neuropathy
Small nerve fibres regulate several key functions such as sweating. Peripheral sympathetic autonomic neuropathy leads to sudomotor dysfunction and dry cracked skin.

Large Fibre Neuropathy
Large nerve fibres neuropathy affects sensory and motor components leading to walking abnormalities and insensate feet. An increasing body of data shows that small fibre damage may precede large fibre damage in diabetic neuropathy.\textsuperscript{22}
Small fibres constitute 70–90% of peripheral nerve fibres and regulate several key functions such as tissue blood flow, temperature and pain perception as well as sweating, all of which are highly relevant to the clinical presentation and adverse outcomes associated with foot ulcerations in patients with diabetes\textsuperscript{22}.

neuropad\textsuperscript{®} response indicates both functional and structural denervation in the feet of diabetic patients. This has considerable clinical relevance in screening for diabetic neuropathy.\textsuperscript{12}

**Sudomotor innervation:** a novel stereologic technique in skin biopies showed a correlation between sweat gland nerve fibre density, neuropathic symptoms, neurological deficits and sweat production.\textsuperscript{22}
neuropad® test vs Intraepidermal Nerve Fibre Density (IENFD)
All diabetic patients with an abnormal neuropad® test had structural denervation of the feet\textsuperscript{12}.

A comparative study of the neuropad® test versus skin biopsies from the dorsum of the foot showed that all diabetic patients with abnormal neuropad® test had significantly lower IENFDs compared to diabetic patients with a normal neuropad® response and healthy subjects\textsuperscript{12}.

neuropad® test vs Non-Contact Corneal Aesthesiometry
Using multi-dimensional scaling, Non-Contact Corneal Aesthesiometry was closer to the Neuropathy Disability Score, Diabetic Neuropathy Symptom Score and neuropad®\textsuperscript{25}.

<table>
<thead>
<tr>
<th>Corneal Sensation threshold (mbars)</th>
<th>Pearson Correlation(.r)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy Disability Score (0-10)</td>
<td>0.2*</td>
<td>0.001</td>
</tr>
<tr>
<td>neuropad® (blue/patchy/pink)</td>
<td>-0.13*</td>
<td>0.032</td>
</tr>
<tr>
<td>Diabetic Neuropathy Symptom Score (0-4)</td>
<td>0.19*</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*spearman rho (ρ)
neuropad® test revealed a sensitivity ≥ 86% and specificity ≥ 67% for the diagnosis of diabetic neuropathy with a cut-off time of 10 minutes comparing a clinical examination (NDS).\textsuperscript{4, 8, 9, 18}

<table>
<thead>
<tr>
<th>N° of patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papanas et al</td>
<td>104</td>
<td>94.4</td>
</tr>
<tr>
<td>Liatis et al</td>
<td>117</td>
<td>86</td>
</tr>
<tr>
<td>Shen et al</td>
<td>98</td>
<td>92.8</td>
</tr>
</tbody>
</table>

The sensitivity of the indicator test for abnormal NCS was 97.8%, and its specificity was 96.4%.\textsuperscript{10} The indicator test has a validity comparable to that of NCS for the diagnosis of diabetic neuropathy.\textsuperscript{10}

<table>
<thead>
<tr>
<th>Clinical Neuropathy Status</th>
<th>with clinical neuropathy (n=83) [n (%)]</th>
<th>without clinical neuropathy (n=37) [n (%)]</th>
<th>( p^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal neuropad\textsuperscript{®}</td>
<td>79 (95.2)</td>
<td>12 (32.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Normal neuropad\textsuperscript{®}</td>
<td>4 (4.8)</td>
<td>25 (67.6)</td>
<td></td>
</tr>
<tr>
<td>Abnormal NCS</td>
<td>78 (94)</td>
<td>14 (37.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Normal NCS</td>
<td>5 (6)</td>
<td>23 (62.2)</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) patients with neuropathy vs patients without neuropathy
Sudomotor Dysfunction diagnosis with neuropad® test provides an earlier diagnosis of Diabetic Neuropathy.\textsuperscript{17,22}

The invariably lower specificity than sensitivity is due to the fact that neuropad® is abnormal in about one third of patients with clinical examination negative for neuropathy. It has been proposed that this result may be ascribed to earlier diagnosis of neuropathy by means of neuropad® before conventional clinical signs become positive.\textsuperscript{24}

neuropad® test positive result in diabetic patients without clinical neuropathy is a remarkable indicator for the development of clinical neuropathy in the future.\textsuperscript{17,22}

This appears to reflect early small fibre involvement which is missed using NDS as a measure of neuropathy.\textsuperscript{22}

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>with neuropathy 2nd examination after 5 years</th>
<th>without neuropathy 2nd examination after 5 years</th>
<th>NDS 1st examination</th>
<th>NDS 2nd examination</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>with normal neuropad® on 1st examination (n=70)</td>
<td>2 (2.86%)</td>
<td>68</td>
<td>2.97 ± 0.72</td>
<td>4.23 ± 0.99</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>with abnormal neuropad® on 1st examination (n=39)</td>
<td>10 (25.64%)</td>
<td>29</td>
<td>3.39 ± 0.91</td>
<td>4.63 ± 1.33</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>
Diabetic patients with abnormal neuropad® test result have higher risk of foot ulceration\textsuperscript{16}

Dryness of the skin of the feet assessed by neuropad® test correlates with foot ulceration.\textsuperscript{16}

A study with 379 patients with diabetes has shown that dryness of the skin of the feet correlates with foot ulceration. Subclinical sudomotor dysfunction can be detected early in diabetes, even in subjects with normal nerve conduction velocities. We showed that dryness of the skin of the feet was detected in 95% of the patients with foot ulceration using the neuropad® test.

An abnormal neuropad® response correlates with foot ulceration in subjects with diabetes. Patients with foot ulceration had more severe peripheral neuropathy and more often an abnormal neuropad® response.

Multivariate statistical analysis demonstrated that patients with diabetes with abnormal neuropad® response are \textbf{16 times} more likely to develop foot ulceration compared to those with a normal neuropad® test result.\textsuperscript{16}

The association (odds ratio, 95% CI) between the studied parameters and foot ulceration by multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>VPT (≥ 25 vs &lt; 25V)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2</td>
<td>NDS (≥ 6 vs &lt; 6)</td>
<td>6.70</td>
<td>3.31-13.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>Monofilament score (&lt;3 vs &gt;3)</td>
<td>6.75</td>
<td>3.27-13.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4</td>
<td>neuropad result (abnormal vs normal)</td>
<td>16.28</td>
<td>6.27-38.24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Early detection of Diabetic Neuropathy and diagnosis of Sudomotor Dysfunction

Screening with neuropad® GP Practice or Self-Testing

Result: NEGATIVE

Status of the feet are OK

Repeat the test within one year

Result: POSITIVE

Sudomotor Dysfunction
- small fibre denervation
- autonomic neuropathy leading to dry skin and callus build (component cause of DFU\(^2^6\))

In case of self testing inform your doctor and start daily treatment with neuropad® repair foot foam

Further examination for sensory neuropathy
- Monofilament
- Vibratip
- Tuning Fork

Repeat once per year

positive

negative

Regular routine feet inspections by the physician. Patient education. no further testing with neuropad® required
The treatment of the symptoms (dry and cracked skin)

The unique and effective combination:
Diagnoses & Management of the feet for patients with Diabetes Mellitus

Complete solution for:
- Effective treatment and management of pathological dry diabetic foot (neuropad® test abnormal).
- Prevention and foot care for patients with Diabetes Mellitus
- Highly user friendly (comfortable in use – 86%, absorbed quickly by the skin – 88%, doesn’t feel fatty – 91%) \(^{19}\)
- A significant beneficial effect was noticeable as early as after 7 treatment days \(^{21}\)
- Effect was enhanced after further 7 treatment days \(^{21}\)
- Paraffin-, vaseline-, lanolin-free: non-comedogenic

Unique combination with 5 active ingredients plus Urea. Covers all aspects for the need of neuropathic skin.

<table>
<thead>
<tr>
<th></th>
<th>10% Urea</th>
<th>Oenothera Biennis Oil (g linoleic Acid)</th>
<th>Extract Centella Asiatica</th>
<th>Panthenol</th>
<th>Alpha Hydroxy Acid AHA-Complex</th>
<th>Allantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exfoliation</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regeneration</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>increases elasticity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Application of moisturizers containing humectants like lactic acid, urea, glycerin and alpha-hydroxy acids is clearly effective in reducing dry skin conditions and enhancing the skin barrier function. \(^{27}\)
An innovative unique standardized diagnostic tool to complete Diabetic Foot Examination. The only simple test for documentation of Sudomotor Dysfunction.

Simple visual indicator test which uses a colour change to define the integrity of skin sympathetic cholinergic innervation.

Benefits of neuropad® test:
- high sensitivity\(^{18,22,23}\) of NDS, ideal for screening
- detects small fibre denervation\(^{12,25,22}\)
- test for sudomotor dysfunction
- non-invasive, direct result
- objective visual test with high reproducibility\(^5\)
- validated for self-examination\(^{11}\)
- easy to use\(^11\), simple, economic
- increases patient`s compliance

neuropad® test results:
Always apply to both feet:

- **pink** = normal result
- **blue/pink** = abnormal result
  - Sudomotor Dysfunction
  - Foot at risk of ulceration
- **blue** = abnormal result
  - Sudomotor Dysfunction
  - Foot at risk of ulceration
References:

5. N. Papanas et al Reproducibility of the New Indicator Test for Sudomotor Function (Neuropad®) in Patients with Type 2 Diabetes Mellitus. Experimental & Clinical Endocrinology Journal 2005; 113 (10): 577 - 581
17. Papanas et al. A Prospective Study on the use of the Indicator Test Neuropad ® for the Early Diagnosis of Peripheral Neuropathy in type 2 Diabetes Exp Clin Endocrinol Diabetes 2010; 118: 1 – 4