Chapter 4

Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score


*Diabetic Medicine, short version, in press.*
Abstract

Aims  Distal polyneuropathy (PNP) is the major risk factor for diabetic foot disease. One of its diagnostic categories is symptom scoring. Several scoring systems are available. The generally accepted Neuropathy Symptom Score (NSS) (17 items) is valid but extensive. We developed, on expert opinion, the 4 item Diabetic Neuropathy Symptom (DNS) score, very manageable but not yet validated. The aim of this study was to validate the DNS-score for diagnosing distal PNP in diabetes.

Methods  In 73 patients, the score characteristics of the NSS and the DNS-score were compared, and construct validity, predictive value and reproducibility were assessed with the Diabetic Neuropathy Examination score, Semmes Weinstein Monofilaments and Vibration Perception Threshold (clinical standards).

Results  43 men and 30 women were studied (mean duration of diabetes 15 years (1-43), mean age 57 years (19-90)). Twenty-four patients had type 1 diabetes, and 49 type 2. Correlation between NSS and DNS-score was high (Spearman r = 0.88). Patients scored more differentiated on the DNS-score. The relation of the NSS and DNS-score, respectively, with the clinical standards was good (Spearman r = 0.21 - 0.60). Both scores had a comparable predictive value. Reproducibility of the DNS-score was good (Cohen weighted Kappa .78-.95). The DNS-score was easier to perform and therefore preferred above the NSS.

Conclusions  The DNS-score is a validated symptom score, fast and easy to perform in clinical practice, with high predictive value to screen for PNP in diabetes.
4.1 Introduction

Distal symmetric polyneuropathy (PNP) is a very common complication of diabetes and is considered to be a major causal factor in the majority of foot ulcers in diabetic patients \(^1,2\). To diagnose PNP, the San Antonio consensus report advises that at least one measurement should be performed in 5 different diagnostic categories \(^3\). One of these categories is symptom scoring. In our opinion, the value of systematic assessment of symptoms is often misunderstood in clinical practice, and is not based on standardised scoring of a specific set of questions. Diagnosis is usually based on Quantitative Sensory Testing or Physical Examination. However, symptoms are important to evaluate, because they reflect the complaints of the patient, they may be of additional diagnostic or prognostic value and treatment might be possible \(^4\).

As diagnostic tests, symptom scores should fulfil the criteria as described by Jaeschke \(^5\). The scores have to be validated (presence of an independent reference standard, adequate spectrum and number of patients, standardisation, soundly based item selection), they should be of predictive value and manageable in clinical practice (reproducibility, performance in clinical practice) \(^5\).

Several scores have been developed to assess symptoms of diabetic neuropathy. The Neuropathy Symptom Score (NSS) \(^4,6-8\) and the Neuropathy Symptom Profile (NSP) \(^9\) both assess diabetic neuropathy. The NSS is the most widely studied and accepted score, and known to be valid and sensitive \(^4,6-8\). The Neuropathy Symptom Profile contains 34 test categories. It is validated and can be read and scored by computer \(^9\). Because both scores assess neuropathy in general, they are rather extensive in clinical practice. The Michigan Neuropathy Screening Instrument (MNSI) \(^10\) and the modified NSS scores of Veves and Young \(^11,12\) have been developed specifically for distal diabetic polyneuropathy. The MNSI is a combination of a symptom score (15 items) and a physical examination score \(^10\). The combination is valid and has a high predictive value. However, there is no separate symptom score, as advised by consensus reports \(^3\). No information is available to review the modifications of the NSS scores of Veves and Young \(^11,12\). The Diabetes Symptom Checklist type 2 (DSC-type 2) \(^13\) and the McGill Pain Questionnaire \(^14\) are scores for diabetes in general and pain, respectively. The DSC-type 2 has been validated both as an entire score and for neuropathy symptoms alone \(^13\). Of the items concerning neuropathy, only numbness and tingling sensations at both hand and feet were associated with other diagnostic standards for diabetic neuropathy \(^15\). The McGill Pain Questionnaire scores for painful diabetic leg problems \(^14\), but no data is available about validity and predictive value. The Diabetic Neuropathy Symptom score (DNS-score), developed at

\[Chapter 4: the DNS-score - 37\]
our hospital, consists of 4 items chosen on clinical relevance and experience, as the most typical and clinically relevant for distal symmetric PNP in diabetes. This score has not been validated or published before.

Because none of these scoring systems fulfil Jaeschke's criteria for diagnostic tests, the aim of this study was to validate the DNS-score for diagnosing distal symmetric PNP in diabetes, and to compare its score-characteristics with the NSS.

4.2 Patients and Methods

Patients:
Our study group consisted of 73 patients with diabetes, covering the entire spectrum of secondary complications. Informed consent was obtained from all participating patients. Exclusion criteria were factors that may interfere with the neurological condition of the subjects other than PNP. Fifty of these 73 patients were randomly selected from the diabetes outpatient clinic of the University Hospital Groningen. The other 23 patients, all known with obvious diabetic foot complications or clinical neuropathy, were selected from the Department of Diabetes at the Rehabilitation Centre Beatrixoord. The characteristics of the 73 patients are shown in Table 1.

Table 1: Patient Characteristics

<table>
<thead>
<tr>
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<th>73</th>
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<tbody>
<tr>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)(SD)</td>
<td>56.9 (16.1)</td>
</tr>
<tr>
<td>Min – max (years)</td>
<td>19 – 90</td>
</tr>
<tr>
<td>Mean duration DM (years) (SD)</td>
<td>14.9 (9.9)</td>
</tr>
<tr>
<td>Min – max (years)</td>
<td>1 – 43</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male – female</td>
<td>43 – 30</td>
</tr>
<tr>
<td>Type DM</td>
<td></td>
</tr>
<tr>
<td>1 - 2</td>
<td>24 – 49</td>
</tr>
<tr>
<td>Mean HbA1c (%) (SD)</td>
<td>8.7 (1.4)</td>
</tr>
<tr>
<td>Min – max</td>
<td>6.6 – 13.5</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>40%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>42%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>38%</td>
</tr>
<tr>
<td>Present or former ulcer</td>
<td>20%</td>
</tr>
</tbody>
</table>
Methods:  
The same researcher (J.-W.G.M.) examined all 73 patients. First, the symptom scores were performed followed by clinical standards; a physical examination score (the Diabetic Neuropathy Examination (DNE) score) and quantitative sensory tests (Semmes Weinstein Monofilaments and vibration perception thresholds), respectively.

1 Symptom Scores

1.1 NSS
The NSS consists of 17 items, 8 focusing on muscle weakness, 5 on sensory disturbances and 4 on autonomic symptoms. Items that are answered negative/absent are scored 0, presence scored as 1 point. Maximum score of the NSS is 17 points.

1.2 DNS-score
An expert panel of the University Hospital (Groningen, the Netherlands) developed a 4 item symptom score for diabetic PNP. The panel consisted of a diabetologist/endocrinologist, a specialist for internal vascular diseases, a neurologist and a physician for rehabilitation medicine; all experienced in diagnosing diabetic neuropathy. The DNS-score consists of the following items: (1) unsteadiness in walking, (2) pain, burning or aching at legs or feet, (3) prickling sensations at legs or feet, and (4) numbness at legs or feet. Presence is scored as 1 point, absence as 0 points, maximum score 4 points. Guidelines to use with the score are shown in Appendix 1.

2 Clinical Standards

The Diabetic Neuropathy Examination (DNE) score, Semmes-Weinstein Monofilaments (SWMF) and Vibration Perception Threshold (VPT) were chosen as clinical standards to study the construct validity of the symptom scoring systems for PNP.

2.1 DNE-score
The DNE-score is a validated, hierarchical physical examination score to diagnose distal symmetric PNP in diabetes. It exists of 8 items; 2 items testing muscle strength, 1 item testing a tendon reflex and 5 items testing sensation. The maximum score is 16 points. A score of > 3 points is defined as disturbed/abnormal.

2.2 Semmes-Weinstein Monofilaments (SWMF)
SWMF’s were tested on the plantar surface of the hallux and central at the heel (when necessary after removal of excessive callus). This method was performed standardised according to generally accepted guidelines.
"yes-no" method was used. This means that the patient says yes each time that he or she senses the application of a monofilament. Six trials were taken, when the patient was unable to respond correct in more than 1 trial, a heavier monofilament was taken. The 1, 10 and 75 gram monofilaments have been used. This resulted in four categories: category 1: 1 gram monofilament felt; category 2: 10 gram felt, 1 gram not felt; category 3: 75 gram felt, 10 gram not felt; category 4: 75 gram not felt. In categories 1 and 2 sensitivity is present, therefore they are scored as normal. Categories 3 and 4 are scored as abnormal.

2.3 Vibration Perception Threshold (VPT)
VPTs were determined using a hand-held biothesiometer (Biomedical Instruments Inc., Ohio, USA). VPT was tested at the dorsum of the hallux on the interphalangeal joint and at the lateral malleolus. It was performed in a standardised way. The voltage of vibration was increased until the patient could perceive a vibration. This was done three times. The mean of these three was used to determine the VPT. Age-adjusted reference values were used. Values higher than the mean+2*SD (reference value) were considered as abnormal.

Reproducibility
In order to test reproducibility of the DNS-score, inter- and intrarater agreement were assessed in a separate study on 10 patients. The 6 women and 4 men, with a mean age of 50.0 years (SD 15.9) had a wide range of neuropathy severity. The mean duration of DM was 11.5 years (SD 10.5); 3 participants had type 1 DM and 7 had type 2 DM. Two doctors, an endocrinologist and a physician for rehabilitation medicine, both experienced in diagnosing diabetic neuropathies, rated these patients twice with an interval of one week.

Statistical Analyses
Internal consistency of the symptom scores was assessed by calculating Cronbach's alpha, and reliability coefficient Rho, which is comparable to alpha. The statistical package SPSS-PC was used to compute the descriptive statistics, reliability coefficient Cronbach’s alpha, Spearman's correlation coefficient r, Student's t-test and ROC curves. Inter- and intrarater agreement was assessed using Cohen’s weighted Kappa.
4.3 Results

In Table 2 general information about the NSS and the DNS-score is shown. The reliability of the DNS-score seems to be a little lower than of the NSS. This is, however, due to the considerable reduction of items, and not to a lower association between the items. Correlation (Spearman r) between these two symptom scores is, as expected, high: .88.

Table 2: Characteristics of the symptom scores.

<table>
<thead>
<tr>
<th></th>
<th>NSS</th>
<th>DNS-score</th>
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<tbody>
<tr>
<td>Mean (SD)</td>
<td>1.9 (2.0)</td>
<td>1.1 (1.3)</td>
</tr>
<tr>
<td>Reliability (alpha)</td>
<td>.74</td>
<td>.64</td>
</tr>
<tr>
<td>Number of items</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Maximum score</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Non used items</td>
<td>4</td>
<td>0</td>
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</table>

Relationship of the NSS and DNS-score with the Clinical Standards
Spearman's correlation coefficient r for the DNE-score with the NSS and DNS-score was similar with values of .56 and .60 (both p<.001), respectively. Spearman's correlation coefficient r for the SWMF with the NSS and DNS-score was .21 (not significant) and .25 (p<.05), respectively. For VPT, Spearman's correlation coefficient r with the NSS and DNS-score was .46 and .56 (both p<.001), respectively.

The NSS and the DNS-score predicted the results of the clinical standards adequately, as shown in Table 3.
Table 3 Relation Clinical Standards - Symptom Scores

group 0= normal on clinical standard, group 1= disturbed on clinical standard

DNE-score:

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<tr>
<th></th>
<th>N</th>
<th>mean NSS (SD)</th>
<th>mean DNS (SD)</th>
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<tbody>
<tr>
<td>0</td>
<td>24</td>
<td>.92 (1.47)</td>
<td>.42 (.93)</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>2.42 (2.07)</td>
<td>1.52 (1.24)</td>
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<td></td>
<td></td>
<td>p .002</td>
<td>p .000</td>
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Semmes Weinstein Monofilaments Hallux:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>mean NSS (SD)</th>
<th>mean DNS (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45</td>
<td>1.42 (1.42)</td>
<td>.84 (1.04)</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>2.64 (2.63)</td>
<td>1.56 (1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p .014</td>
<td>p .019</td>
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</table>

Vibration Perception Threshold Hallux:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>mean NSS (SD)</th>
<th>mean DNS (SD)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>39</td>
<td>1.28 (1.47)</td>
<td>.67 (.98)</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>2.63 (2.34)</td>
<td>1.69 (1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p .004</td>
<td>p .000</td>
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Sensitivity / Specificity

Figure 1 shows the ROC-curves of, respectively, the NSS and DNS-score as compared with the DNE-score. For NSS and DNS-score the areas under the curve are .75 and .78, respectively. Using the SWMF at the hallux these values are .62 and .65, respectively; and using VPT .68 and .73, respectively. At a cut off point of 0 versus 1-4 for the DNS-score, sensitivity was 79% and specificity 78% regarding the DNE-score. Regarding SWMF sensitivity was 81% and specificity 56%, for VPT sensitivity was 81% and specificity 58%.
Figure 1: ROC-curves of NSS and DNS-score, respectively, in relation to the DNE-score.

Reproducibility of the DNS-score

The intrarater agreement showed Cohen’s weighted Kappa’s for both raters of .89 and .78, the interrater agreement on two occasions was .95, and .83, respectively, indicating a good to very good level of agreement\textsuperscript{25,26}.
4.4 Discussion

The NSS is a validated and widely accepted symptom score for diabetic neuropathy \(^4,\,6-8\). The most frequent form of neuropathy in diabetes and major risk factor for diabetic foot disease is distal symmetric PNP \(^1\). Several items of the NSS are seldom scored, because the NSS has not been developed specifically for distal PNP. Large groups of diabetic patients need to be screened regularly to diagnose PNP early as part of prevention of diabetic foot ulcers. Consequently, several other scoring systems and modifications have been developed, but they do not sufficiently fulfil all the criteria necessary for adequate diagnostic tests. In this study, the DNS-score was validated with the aim of achieving a manageable symptom scoring system for diagnosing distal symmetric diabetic PNP in clinical practice and epidemiological studies.

We compared the score-characteristics of the DNS-score with the original NSS. Furthermore, the construct validity of the NSS and DNS-score has been studied by comparing the scores with the clinical standards chosen: the DNE-score, SWMF and VPT. We conclude that both symptom scores adequately fulfil the criteria for diagnostic tests, as mentioned in the introduction. We prefer the DNS-score for further use as symptom score, because the differences between the scores on validity and predictive value are small and not clinically relevant, and the manageability of the DNS-score is excellent. Consisting of only 4 items, the DNS-score is fast and easy to perform in clinical practice with a high reproducibility.

Diagnostic tests can be discriminative (diagnosis), predictive (prognosis) or evaluative (follow up). The DNS-score is validated with clinical standards on discriminative and predictive values. For evaluation of treatment or follow up, the score might be too short with only four items. However, in the NSS the number of items related to PNP is also very limited. Unfortunately the exact weight of the different categories, individual or in combination, in diagnosing diabetic PNP and predicting diabetic foot complications, is not yet known.

Sensitivity and specificity of the DNS-score were high regarding the DNE score, SWMF and VPT. Because the DNS-score will be used for screening purposes, sensitivity is preferred above specificity. A score of 1 or more points on the DNS-score is very sensitive for presence of diabetic PNP. In combination with the results of the other diagnostic categories of the San Antonio Consensus, this gives an indication of type and severity of PNP.
Controversy exists about the use of symptom scoring in diagnosing PNP in diabetes. Because symptoms of neuropathy (pain, numbness and tingling) are present in 30-40% of all people with diabetes, Mayfield et al. concluded that the presence or absence of symptoms should not be used to assess the risk of ulcers or amputation. Valk et al. found that symptoms of neuropathic pain and paraesthesia were neither correlated with the results of physical examination nor with the results of neurophysiological examination. In another study they concluded that only symptoms of numbness and tingling sensations in hand and feet (items of the DSC-type 2), were associated with the clinical examination, but not with neurophysiological examination. Franse et al. studied whether a patient history could replace the Clinical Neurological Examination (CNE). The individual symptoms were insufficiently predictive for the presence of polyneuropathy. They concluded that individual symptoms could not replace the CNE. Dyck et al. found an association between complaints of diabetic neuropathy, abnormalities of the clinical examination and abnormalities of nerve conduction. In our report significant and clinically relevant correlations have been shown between the symptom scores and the DNE-score, SWMF and VPT, respectively; which are all accepted tests with known predictive value for diabetic foot complications. Therefore, as the consensus advises, we state that symptom scoring deserves to be a part of the diagnostic set, complementary to other diagnostic categories for diabetic PNP.

It is known that the reliability of symptom scores may be poorer than the reliability of the other diagnostic categories. This might be caused by the subjectivity of the scores, leading to a poor reproducibility. The consensus advises to score dichotomous to enhance reliability. In the DNS-score, a short and dichotomous symptom score, the reproducibility is high.

In conclusion, the DNS-score, a symptom score specific for distal symmetric PNP in diabetes, has now been validated, and is fast and easy to perform in clinical practice. As the consensus advises, this scale has to be used complementary to other diagnostic categories as for example standardised physical examination (for example the DNE-score) and quantitative sensory testing. Further prospective studies are necessary with the DNS-score, the DNE-score and other diagnostic tests, to assess the predictive value of the scales and items.
4.5 References

Appendix 1: DNS-score

DNS-score and guidelines

1 Are you suffering of unsteadiness in walking?
need for visual control, increase in the dark, walk like a drunk man, lack of contact with floor
remark: it is assumed that the patient has no limiting visual, hearing or central neurological deficits.

2 Do you have a burning, aching pain or tenderness at your legs or feet?
remark: it is assumed that intermittent claudication has been made unlikely by excluding pain which develops during walking and disappears upon halting, and that ischaemic rest pain is made unlikely by lack of effect of dependency, in both cases further supported by the lack of absent foot-ankle pulsation and/or reduced ankle- and toe pressures.

3 Do you have prickling sensations at your legs and feet?
occurring at rest or at night, distal>proximal, stocking glove distribution

4 Do you have places of numbness on your legs or feet?
Distal>proximal, stocking glove distribution

The questions should be answered "yes" (positive: 1 point) if a symptom occurred more times a week during the last 2 weeks or "no" (negative: no point) if it did not.
Max. score: 4 points
0 points: PNP absent
1-4 points: PNP present
50 - The diabetic foot syndrome