The diabetic foot syndrome, diagnosis and consequences
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 6

Clinical diagnosis of diabetic polyneuropathy with the DNS and DNE score


Submitted.
Abstract

Objective The discriminative power of the Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) score for diagnosing diabetic PNP, and their relation with cardiovascular Autonomic Function Testing (cAFT) and Electro Diagnostic Studies (EDS) are evaluated.

Methods Three groups (matched for age and sex) were selected: 24 diabetic patients with neuropathic foot ulcers (diabetes ulcus group), 24 diabetic patients without clinical neuropathy or ulcers (diabetes control group) and 21 controls without diabetes (controls). In all participants the DNS- and DNE-score were assessed, and cAFT (Heart Rate Variability (HRV) and Baro Reflex Sensitivity (BRS)) and EDS were performed (Nerve Conduction Sum (NCS) score; muscle fiber conduction velocity: fastest/slowest ratio (F/S ratio)).

Results Both the DNS and the DNE score discriminated between the diabetes ulcer and diabetes control group significantly (p<.001). The DNE score even discriminated between the diabetes control group and controls without diabetes (p<.05). Spearman's correlation coefficients between both DNS- and DNE-score and cAFT (HRV -.42 and -.44, respectively; BRS -.30 and -.29, respectively) and EDS (NCS .51 and .62, respectively; F/S ratio .44 and .62, respectively), were significant. Odds ratios were calculated for both DNS and DNE score with cAFT (HRV 4.4 and 5.7, respectively; BRS 20.7 and 14.2, respectively) and EDS (NCS 5.6 and 16.8, respectively; F/S ratio 7.2 and 18.8, respectively).

Conclusions the DNS and DNE scores are capable to discriminate between patients with and without PNP, and are strongly related to cAFT and EDS. This further confirms the strength of the DNS and DNE scores in diagnosing diabetic PNP in daily clinical practice.
6.1 Introduction

One of the major risk factors for the development of diabetic foot complications is distal symmetric sensorimotor polyneuropathy (PNP) \(^1,^2\). For diagnosing PNP, no gold standard is available. The San Antonio consensus panel has recommended that at least 1 measurement should be performed in 5 different diagnostic categories \(^3\). These are symptom scoring, physical examination scoring, Quantitative Sensory Testing (QST), cardiovascular Autonomic Function Testing (cAFT) and Electro-Diagnostic Studies (EDS). Because none of the existing symptom and physical examination scores for diabetic PNP completely fulfilled methodological criteria for diagnostic tests, the Diabetic Neuropathy Symptom (DNS) score and Diabetic Neuropathy Examination (DNE) score were developed \(^4,^5\). The construct validity of these scores was studied in relation to Semmes Weinstein monofilaments and Vibration Perception Threshold testing (both forms of QST), because of their known predictive value to the development of diabetic foot complications \(^6-^9\). cAFT has an important prognostic value for the prediction of diabetic foot complications \(^8,^10,^11\) and mortality due to cardiovascular problems \(^12,^13\). The prognostic value of EDS is less clear, although EDS is supposed to be the most sensitive diagnostic tool for diabetic PNP \(^14\). The relation between the DNS- and DNE-scores and cAFT and EDS, respectively, has not yet been studied.

The objective of this study is to assess the discriminative power of the DNS- and DNE-scores for diagnosing diabetic PNP, and their relation with cAFT and EDS, respectively.

6.2 Patients and Methods

Patients

All participants were recruited from the Diabetes Outpatient Clinic (University Hospital Groningen) and from the Rehabilitation Centre Beatrixoord Haren, after informed consent. To study the discriminative power of the DNS- and DNE-score, three groups of subjects were studied. Selection was performed by checking the patient records. The first group consisted of 24 diabetic patients known with previous or present neuropathic foot ulcers (group DU). These ulcers were purely neuropathic by origin, as was confirmed by their localization (plantar surface of the foot at high pressure points), and by absence of peripheral arterial disease as described below. In the second group, 24 diabetic patients unknown with clinical neuropathy or foot ulcers (group DC) were included, this was confirmed by normal sensitivity to the 10 gram Semmes Weinstein Monofilament testing (performance as described previously) \(^5\). The third group consisted of 21
control subjects with normal glucose tolerance (group C). All groups were matched for sex and age (within 5 yrs), and the diabetic groups for duration and type of diabetes (type 1/ type 2; type 1 DM was considered on clinical grounds when the onset of the disease was an ketoacidosis or before the age of 40 years) as well. Subjects with a history of or clinically apparent cardiac disease, electrocardiographic abnormalities or using betablockers or calcium antagonists were excluded. Peripheral arterial disease was excluded by normal ankle-arm indices (>0.90), toe-arm indices (>0.70) and normal plethysmography (crest time 0.22 sec) in all groups. Normal glucose tolerance of the control subjects was demonstrated by a fasting capillary blood glucose < 6.1 mmol/l and a blood glucose < 7.8 mmol/l 2h after a 75 gr oral glucose tolerance test. Details of the clinical characteristics of each group are given in Table 1.

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DU (n=24)</th>
<th>DC (n=24)</th>
<th>C (n= 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age (years)</td>
<td>57.3 ± 11.4</td>
<td>52.2 ± 12.0</td>
<td>58.2 ± 9.9</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>14/10</td>
<td>13/11</td>
<td>10/11</td>
</tr>
<tr>
<td>mean duration of diabetes (years)</td>
<td>16.9 ± 12.0</td>
<td>13.1 ± 9.8</td>
<td></td>
</tr>
<tr>
<td>type of diabetes (type 1/type 2)</td>
<td>5/19</td>
<td>8/16</td>
<td></td>
</tr>
<tr>
<td>mean HbA1c (%)</td>
<td>8.3 ± 1.1</td>
<td>7.5 ± 0.8</td>
<td></td>
</tr>
</tbody>
</table>

DU: diabetic patients with neuropathic ulcer; DC: diabetic patients without neuropathy; C: controls; Data are means ± SD, or n.

Methods
The DNS- and DNE-score (EB), cAFT (JL) and EDS (JH) were performed by different researchers, blinded for the group to which the participant was allocated. The researchers were acting independently and no information about the results was exchanged during the study. An overall neuropathy sum score, according to the San Antonio consensus, was composed.

Diabetic Neuropathy Symptom (DNS) score
Both the DNS-score and DNE-score have been described in detail elsewhere. Both the DNS score and DNE score have been described in detail elsewhere. In short, the DNS score is a 4 item validated symptom score, with high predictive value to screen for PNP in DM. Symptoms of unsteadiness in walking, neuropathic pain, paraesthesia and numbness are elicited. The
presence of a symptom is scored as 1 point; the maximum score is 4 points. A score of one or higher is defined as positive for PNP.

**Diabetic Neuropathy Examination (DNE) score**

The DNE-score is a sensitive and validated hierarchical scoring system. The score contains 2 items concerning muscle strength, 1 concerning reflexes and 5 concerning sensation, with a total of 8 items. Each item is scored from 0 to 2 (0 is normal and 2 severely disturbed). The maximum score is 16 points. A score of more than 3 points is defined as positive for PNP.

**cardiovascular Autonomic Function Testing (cAFT)**

Cardiovascular autonomic function was assessed by analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS). All participants were studied in the morning. All measurements took place in a quiet room with the temperature kept constant at 22°C. Blood pressure was monitored by a Finapres (Ohmeda 2300, Inglewood, Col., USA) and heart rate by an ECG monitor (Hewlett-Packard 78351T, Palo Alto, Ca., USA). After 30 min of supine rest, the Finapres and ECG signal were sampled at 100 Hz and stored on a personal computer during 15 min. Offline, 300 seconds of each recording was analyzed by the CARSPAN program (IEC ProGamma, Groningen, the Netherlands), as described previously. After artifact correction and stationarity check, discrete Fourier transformation of systolic blood pressure and RR interval length was performed. HRV analysis was performed in accordance with the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. The total power frequency band (TP) of HRV was defined as 0.02-0.40 Hz. Because no reference values of HRV are available, the median of the control group was used, 9.2 ln(ms²). BRS was determined by the transfer function method and defined as the mean modulus between systolic blood pressure and heart rate variability in the 0.07-0.14 Hz frequency band with at least 0.5 coherence, expressed in ms/mmHg. A BRS lower than 3 ms/mmHg leads to high mortality rates in chronic heart failure and after myocardial infarction, in diabetes the prognostic value of the BRS is not yet known. In this study, a BRS < 3 ms/mmHg was considered as indicative for cardiovascular autonomic neuropathy.

**Electro-Diagnostic Studies (EDS)**

Nerve conduction studies were performed with standard surface stimulation and recording techniques using an electromyograph type Nicolet Viking IIe and IV with standard filter settings. All measurements were performed after warming in hot water (38°C) of fore arm and lower leg during at least 15 minutes. Peak-peak amplitudes were used. Motor Nerve Conduction Velocity (MNCV) and amplitudes were measured in the left median (thenar) and
peroneal nerves (tibialis anterior). Sensory Nerve Conduction Velocities and amplitudes were measured antidromically with ring electrodes placed around the middle finger (median nerve) and stimulation lateral of the Achilles tendon (sural nerve). An overall Nerve Conduction Sum (NCS) score was defined as the number of these four nerves with an abnormal conduction velocity and amplitude, ranging from 0 (all normal) to 4 (all abnormal). Reference values from our own laboratory were used, see legend table 2. Invasive MFCV (I-MFCV) measurements were performed in the tibialis anterior muscle at rest by means of needle electrodes adapted from the method as described previously \(^2\). In short, muscle fibers were stimulated in the distal part of the tibial anterior muscle directly by a small monopolar needle electrode (cathode) using a surface electrode as anode. Filter settings 500 Hz-10 kHz, stimulation 0.2 ms, 1-2 mA. The resulting muscle fiber action potentials were detected at a known distance (50-60 mm) by a small concentric needle electrode. With this technique, action potentials supposed to represent individual muscle fibers were identified, and the resulting conduction velocities were calculated. As parameters the mean I-MFCV and the fastest/slowest ratio representing the scatter of conduction velocities were used and compared to normative values from our own laboratory.

**Neuropathy Sum score**
For this study, an overall score was composed of the 5 diagnostic categories of the San Antonio consensus: DNS-score (symptom score), DNE-score (examination score), BRS (cAFT) and NCS (EDS). Because SW-MF testing was used in patient selection, these data, representing QST as the fifth category of the San Antonio consensus \(^3\), were also available. These 5 tests together formed the Neuropathy Sum score. For each abnormal test result 1 point was given, the maximum score is 5 points.

**Statistics**
The statistical package SPSS-PC 10.0 was used to compute the descriptive statistics, ANOVA, Chi-Square tests, independent samples t-test, Spearman's correlation coefficient and Odds Ratio's. Unless otherwise indicated, mean and SD are given. A p-value < .05 was considered statistically significant.

### 6.3 Results

Table 1 shows the patient characteristics. There were no significant differences between the groups for mean age (p= 0.15) and sex (p= 0.77) and for the DU and DC groups for the duration (p= 0.23) and type of diabetes (p=0.33). The mean HbA1c of the DC group was significantly lower (p<0.01) than of the DU group.
Results of DNS- and DNE-score for the 3 groups

For the DNS-score, the scores (SD) of the DU, DC and C group are 2.29 (1.23), .44 (.84) and .38 (.74), respectively. Differences between DU and both DC and C, respectively, were significant, p<0.001 in both cases, but not between DC and C.

For the DNE-score, the scores (SD) of the DU, DC and C groups are 8.90 (1.98), 1.46 (2.02), and .43 (.81), respectively. Significant differences were found in all comparisons of the 3 groups, between DU and both DC and C groups, respectively, p<0.001 in both cases, and differences between DC and C p<0.05.

Table 2: Results of the tests for PNP for the 3 groups

<table>
<thead>
<tr>
<th>Test</th>
<th>DU (n=24)</th>
<th>DC (n=24)</th>
<th>C (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNS (% ≥ 1 points = abnormal)</td>
<td>96%</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>DNE (% &gt; 3 points = abnormal)</td>
<td>100%</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>NCS (% ≥ 1 points = abnormal)</td>
<td>85%</td>
<td>32%</td>
<td>15%</td>
</tr>
<tr>
<td>F/S ratio (% &gt; 1.9 = abnormal)</td>
<td>91%</td>
<td>33%</td>
<td>10%</td>
</tr>
<tr>
<td>BRS (% &lt; 3 ms/mmHg)</td>
<td>52%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>HRVtp (% &lt; median)</td>
<td>95%</td>
<td>57%</td>
<td>50%</td>
</tr>
<tr>
<td>Neuropathy Sum score (% ≥ 1 point)</td>
<td>100%</td>
<td>47%</td>
<td>40%</td>
</tr>
</tbody>
</table>

DU: diabetic patients with neuropathic ulcer; DC: diabetic patients without neuropathy; C: controls.

DNS  Diabetic Neuropathy Symptom score
DNE  Diabetic Neuropathy Examination score
NCS  Nerve Conduction Sum score (ref value own laboratory)
F/S ratio  Fastest/Slowest Ratio of Muscle Fiber Conduction Velocity (ref value own laboratory)
BRS  Baro Reflex Sensitivity
HRVtp  total power of Heart Rate Variability (abnormal defined as < median control group)
Results of the PNP tests

Table 2 shows the % of patients of the 3 groups who scored abnormal on the individual diagnostic tests and on the Neuropathy Sum score. The DNS- and DNE-score correctly identified the DU group in 96 and 100%, respectively, and the healthy controls in 76 and 100%, respectively. Almost a half (47%) of the patients of the DC group and 40% of the C group scored at least 1 point on the Neuropathy Sum score, which means that they scored abnormal on at least 1 diagnostic category of the San Antonio consensus. Table 3 shows the specified results on the Neuropathy Sum score.

Table 3: The results on the Neuropathy Sum (NS) score for the 3 groups.

<table>
<thead>
<tr>
<th>NS score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DU (22)</td>
<td></td>
<td>12</td>
<td>1</td>
<td>12</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>DC (23)</td>
<td>12</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (20)</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DU: diabetic patients with neuropathic ulcer; DC: diabetic patients without neuropathy; C: controls

Relation of the DNS- and DNE-score with cAFT and EDS

In Table 4 the relation of the DNS and DNE scores with cAFT (BRS and HRV) and EDS (NCS and I-MFCV) is shown. Furthermore, the Odds ratios are shown of these tests.
Table 4: Correlation (Spearmans' rho) and Odds Ratios (95% confidence interval) of DNS-score and DNE-score with EDS and cAFT respectively.

<table>
<thead>
<tr>
<th></th>
<th>DNS</th>
<th>DNE</th>
<th>NCS</th>
<th>BRS</th>
<th>F/S</th>
<th>HRVtp</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DNE</td>
<td>42.7 (8.4-21.5)</td>
<td>16.8 (3.8-74)</td>
<td>18.8 (5.0-71)</td>
<td>14.2 (2.8-74)</td>
<td>5.7 (1.8-17.8)</td>
<td>4.4 (1.5-12.8)</td>
</tr>
<tr>
<td>NCS</td>
<td>5.6 (1.7-18.2)</td>
<td>18.8 (5.0-71)</td>
<td>13.9 (3.6-53)</td>
<td>4.0 (0.7-24.4)</td>
<td>4.4 (1.3-14.7)</td>
<td>5.7 (1.8-17.8)</td>
</tr>
<tr>
<td>BRS</td>
<td>7.2 (2.3-22.3)</td>
<td>14.2 (2.8-74)</td>
<td>4.0 (0.7-24.4)</td>
<td>3.0 (0.7-11.7)</td>
<td>4.6 (1.5-14.2)</td>
<td>4.4 (1.3-14.7)</td>
</tr>
<tr>
<td>F/S</td>
<td>20.7 (2.5-172)</td>
<td>14.2 (2.8-74)</td>
<td>4.0 (0.7-24.4)</td>
<td>3.0 (0.7-11.7)</td>
<td>4.6 (1.5-14.2)</td>
<td>4.4 (1.3-14.7)</td>
</tr>
<tr>
<td>HRVtp</td>
<td>4.4 (1.5-12.8)</td>
<td>5.7 (1.8-17.8)</td>
<td>4.4 (1.3-14.7)</td>
<td>5.7 (1.8-17.8)</td>
<td>4.4 (1.5-12.8)</td>
<td>5.7 (1.8-17.8)</td>
</tr>
</tbody>
</table>

* p < .05; ** p < .001; ns: not significant.

Diabetic Neuropathy Symptom (DNS), Diabetic Neuropathy Examination (DNE), Nerve Conduction Sum score (NCS), Baro Reflex Sensitivity (BRS), total power of Heart Rate Variability (HRVtp), Fastest/Slowest Ratio of Muscle Fiber Conduction Velocity (F/S).
6.4 Discussion

This study shows that the DNS- and DNE-score are capable to differentiate between subjects with and without neuropathy in diabetes. Previously, the construct validity of both scores already has been studied in relation to Semmes Weinstein Monofilaments and Vibration Perception Threshold testing, both Quantitative Sensory Tests known to be strong predictors of the development of diabetic foot complications. In this report, the DNS- and DNE-score are further validated with the Electro Diagnostic Studies (EDS) and cardiovascular Autonomic Function Testing (cAFT). There was a strong relation between the DNS- and DNE-score and EDS, both with nerve and muscle fiber conduction studies. Furthermore, the relation of the DNS- and DNE-score with cAFT was significant, although this was stronger for HRV than for BRS for both scores. These results further confirm the strength of the DNS- and DNE-score in diagnosing diabetic polyneuropathy.

HRV and BRS are advanced measures, able to detect early abnormalities in cAFT. The relation of HRV with the parameters for PNP (DNS- and DNE-score, NCS, F/S ratio of MFCV) was stronger than for BRS. While HRV measures the efferent part of the baroreflex arc, i.e. vagal and sympathetic nerve-mediated modulation of heart rate, BRS measures the relation between input (blood pressure sensed at the carotid arteries and aorta baroreceptors) and the output (modulations of heart rate, myocardial contractility and peripheral arterial resistance) of the baroreflex. Thus, the differences in HRV and BRS in relation to diabetic PNP may be due to the fact that BRS assesses different aspects of cardiovascular reflex function than HRV. Interestingly, it has also been proposed that PNP and cAFT are distinct entities with a different pathogenesis, thereby explaining the previously noticed variable relation between cAFT and PNP.

The Odds ratios for the DNS- and DNE-score, respectively, with NCS, MFCV (F/S ratio), HRV and BRS are high, which means that the DNS- and DNE-score are capable to predict the results of these other diagnostic tests. Performing the DNS- and DNE-score at the outpatient clinic gives a good clue about the necessity of performing these, more laborious, expensive and less patient friendly, laboratory tests. However, in our opinion, the necessity of complementary performance of cAFT and EDS next to the DNS- and DNE-score as proposed in the San Antonio consensus, is debatable in clinical practice. No specific therapeutic interventions are available for neuropathy besides strict diabetes regulation, symptomatic treatment of, for example, neuropathic pain, prevention and instruction. For screening, prevention and instruction, the performance of the DNS- and DNE-score, eventually in combination with QST, may be sufficient.
As expected, performance of these various tests for diabetic PNP shows large percentages of abnormality among the group of patients with neuropathic ulcers. Although the percentage with abnormal BRS is rather low compared with the percentages of the other tests, these patients are expected to have a very poor prognosis due to their high risk of cardiovascular complications \(^{19,20}\). In their treatment, hospitalisation and rehabilitation programme, this should be taken into account. Strikingly, 48% of this group with obvious neuropathy, has a BRS > 3 ms/mmHg. This supports the hypothesis that cAFT might develop differently from PNP, as an independent complication of diabetes.

In both the diabetes group without neuropathy and the control group, abnormal tests results were found for most tests. This might be caused by lack of specificity of the tests, as shown in the control group, although it also shows that after careful and sensitive screening more abnormalities can be found, also in diabetic patients unknown with neuropathy, as expected after checking the records. The results of the DNS-score and the Neuropathy Sum score are most striking. In our previous DNS-score validation, we chose a cut-off value of $\geq 1$ to define a sensitive measure for diabetic PNP. Our present values show that almost a quarter of our control group scores abnormal. The same problem will exist for other symptom scores, such as for example the NSS \(^{14,23}\), because these scores do also score these four items of the DNS-score. The Neuropathy Sum score, based on the 5 diagnostic categories as advised by the San Antonio consensus \(^3\), also shows high percentages of participants, even in the control group, with abnormal test results. Therefore, one should consider the risk of overdiagnosis by using all 5 the diagnostic categories of the San Antonio consensus. Further research should be done to characterise an optimal set of diagnostic categories for diabetic PNP.

In conclusion, this report shows that the DNS- and DNE-score allow to discriminate between patients with and without diabetic PNP. Both scores are strongly related to electrodiagnostic studies and cardiovascular autonomic function testing. These results, together with the previously published results of the validation of both scores, further confirm the strength of the DNS- and DNE-score in diagnosing diabetic polyneuropathy in clinical practice.
6.5 References

The diabetic foot syndrome