# Subjective versus objective assessment of painful diabetic peripheral neuropathy

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**Introduction**
Diabetic peripheral neuropathy (DPN) is one of the commonest chronic complications of diabetes mellitus. It is documented that 26.4% of the cases with type 2 diabetes mellitus have painful DPN, whereas approximately half of the DPN cases may not have symptoms. Although neurophysiologic studies represent an objective and sensitive tool in the diagnosis of diabetic neuropathy, they remain limited owing to many factors; thus, there is a need to develop simpler tools that can fit into this gap, hence the development of different neuropathy scores.
**Aim**
To evaluate different tools and methods either subjective or objective in diagnosis of painful DPN in type 2 diabetic patients.
**Patients and methods**
We included 200 cases with type 2 diabetes mellitus recruited from the diabetes and diabetic neuropathy clinics in Mansoura Specialized Medical Hospital fulfilling the inclusion and exclusion criteria. They were divided into two groups: group 1 included 150 diabetic cases with painful peripheral diabetic neuropathy, and group 2 included 50 diabetic cases without neuropathy.
**Results**
Glycated hemoglobin was significantly elevated in the peripheral neuropathy group compared with the other group (8.24 vs. 7.27%; $P<0.001$). Regarding neutrophil/lymphocytic ratio in our study, it was not significantly different between the two groups ($P=0581$). It had mean values of 2.17 and 2.1 in groups 1 and 2, respectively.
**Conclusion**
Higher grades of the scores performed in this study were associated with a severe form of neuropathy. Both duration of diabetes and glycated hemoglobin levels had a significant positive correlation with these scores. Regarding neutrophil/lymphocytic ratio in our study, it did not show a significant difference between the two groups.

**Keywords:**
diabetic peripheral neuropathy, glycated hemoglobin, neutrophil/lymphocytic ratio

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## Background

Peripheral neuropathy (PN) is one of the most common complications of type 2 diabetes mellitus (T2DM). Approximately 22% of the diabetic cases experience PN, which was graded as severe or moderate. Long-standing pain related to PN takes place in one of six patients experiencing DM [1].

PN can present as numbness, tingling, and altered pain sensation, which can lead to damage to the skin, leading to neuropathic ulcers, and it is a leading cause of amputation. Additionally, proximal diabetic neuropathy causes painful muscle atrophy and weakness [2].

Diabetic peripheral neuropathy (DPN) has been defined as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.' It can be widely divided into asymmetric (multifocal and focal) neuropathy and generalized symmetric polyneuropathy [3].

DPN of the limbs increases with both age and duration of diabetes and seems more common in those with suboptimal glycemic control and obesity. Approximately half of the cases, however, may have no symptoms. Commonly documented symptoms in DPN could be painful (positive) symptoms or nonpainful (negative) symptoms [4].

Different systems of clinical scoring are used for DPN screening. They can improve the accuracy of diagnosis as the patients' findings of examination from dissimilar simple tests of screening are combined into a composite score of examination. All cases should have DPN screening at the T2DM diagnosis and 5 years after the type 1 diabetes mellitus (T1DM) diagnosis and should undergo more than or equal to one of the subsequent tests every year: temperature, pinprick, vibration or pressure sensation, and ankle reflex. Combinations of more than or equal to 1 test may assist in better detection of DPN. Any neuropathic symptom history should be obtained, and a cautious lower limb and feet examination should be carried out. Nerve conduction study and other causes of exclusion are infrequently required, except when the DPN diagnosis requires confirmation [5].

## Aim

The aim of the study is to evaluate different tools and methods either subjective or objective in diagnosis of painful DPN in type 2 diabetic patients.

## Patients and methods

### Procedure

*Study design*

This is a case–control study that was conducted during the period of 1 year (from March 2019 till February 2020) in Mansoura Specialized Medicine Hospital diabetes and diabetic neuropathy clinics, Mansoura University Hospitals, Mansoura University, Egypt.

A total of 200 cases presented with type 2 diabetes were included in the current study ($n$=200). They were divided into two groups: group 1, which included 150 diabetic cases who had painful peripheral diabetic neuropathy, and group 2, which included 50 diabetic cases who had no neuropathy as a control group.

The inclusion criteria include any type 2 diabetic patient above 18 years with and without diabetic neuropathy, whereas exclusion criteria included pregnancy, critically ill diabetic patients, thyroid dysfunction, Cushing syndrome, acromegaly, and chronic liver disease. An informed consent was obtained from all cases before participating in the study. This research was approved by Institutional Review Board (IRB), Mansoura Faculty of Medicine, Mansoura University.

Data were collected as full history and examination, including age, sex, BMI, duration of diabetes and its regimen of treatment, and presence or absence of hypertension (HTN). Presence or absence of neuropathy was assessed using neuropathy symptom score (NSS), neuropathy disability score (NDS) [6], Michigan neuropathy screening instrument (MNSI) [7], Toronto clinical scoring system (TCSS) [8], and Utah early neuropathy scale (UENS) [9].

All the 200 patients were subjected to a nonfasting blood sample, and the following was measured: complete blood count was done by fully automated cell counter (Sysmex XP 300, Sysmex Corporation, Kobe, Hyogo, Japan) and then the ratio between neutrophil and lymph was calculated. Glycated hemoglobin (HbA1C) was assessed by HPLC technology on Tosoh G8 (Tosoh Corporation, Tokyo, Japan). Neutrophil/lymphocyte ratio (NLR) was assessed. The white blood cell count was calculated in a sample of blood which was collected in tripotassium (K3) EDTA (7.2 mg) tubes and underwent analysis within 120 min of venipuncture by an automatic blood counter [10].

The collected data were analyzed by using the statistical package for social sciences (SPSS/PC/ VER 17, IBM Corporation Business Analytics Software portfolio).

## Results

Analysis of the demographic data showed that there was no significant difference between the two groups regarding age ($P$=0.166). The mean age of the included cases was 54.94 and 52.7 years in groups 1 and 2, respectively. Moreover, no significant difference was detected between the two groups regarding sex ($P$=0.203). Females represented 66 and 56% of cases in groups 1 and 2, respectively, whereas the remaining cases were males (Table 1).

There was a significant difference between the study groups regarding duration of DM ($P$<0.001). It was significantly longer in the PN group (median 11 vs. 6 years in non-neuropathy group). Insulin was commenced for 65.3 and 48% of cases in groups 1 and 2, respectively, whereas the remaining cases had oral antidiabetics. There was an increased insulin administration in the PN group ($P$=0.03) (Table 1).

There was no significant difference between the two groups regarding the prevalence of obesity ($P$=0.935). Obese individuals represented 49.3 and 50% of cases in groups 1 and 2, respectively. Regarding HTN, it was significantly more prevalent in the neuropathy group (75.3 vs. 48% of cases in the other group – $P$<0.001) (Table 1).

**Table 1 Comparison of demographic, clinical, and laboratory data among studied groups**

| Variables | Patient group (*N*=150) | Control group (*N*=50) | Test of significance | *P* value |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean±SD | 54.94±10.16 | 52.70±8.93 | *t*=1.39 | 0.166 |
| Minimum–maximum | 24–79 | 25–70 | | |
| ≤40 | 15 (10.0) | 8 (16) | | |
| 40–60 | 98 (65.3) | 30 (60) | | |
| >60 | 37 (24.7) | 12 (24) | $\chi^2$=1.34 | 0.510 |
| Sex [*n* (%)] | | | | |
| Male | 51 (34.0) | 22 (44) | $\chi^2$=1.62 | 0.203 |
| Female | 99 (66.0) | 28 (56) | | |
| Duration of DM (years) | | | | |
| Median (minimum–maximum) | 11 (2–50) | 6 (1–21) | *Z*=4.97 | ≤0.001* |
| ≤10 | 74 (49.3) | 45 (90) | | |
| >10 | 76 (50.7) | 5 (10) | $\chi^2$=25.73 | ≤0.001* |
| Treatment [*n* (%)] | | | | |
| Insulin | 98 (65.3) | 24 (48) | $\chi^2$=4.73 | 0.03* |
| Oral | 52 (34.7) | 26 (52) | | |
| Obesity [*n* (%)] | | | | |
| Obese | 74 (49.3) | 25 (50) | $\chi^2$=0.007 | 0.935 |
| Nonobese | 76 (50.7) | 25 (50) | | |
| HTN [*n* (%)] | | | | |
| Yes | 113 (75.3) | 24 (48) | $\chi^2$=12.98 | ≤0.001* |
| No | 37 (24.7) | 26 (52) | | |
| HbA1C | 8.24±1.66 | 7.27±1.67 | 3.62 | ≤0.001* |
| NLR | 2.17±0.79 | 2.10±0.83 | 0.553 | 0.581 |

DM, diabetes mellitus; HbA1C, glycated hemoglobin; HTN, hypertension; NLR, neutrophil/lymphocyte ratio. t: Student *t* test. $\chi^2$: $\chi^2$ test. *Z*: Mann–Whitney test. *Significant *P* value less than or equal to 0.05

**Table 2 Subjective scores among the neuropathy group**

| Subjective scores | Neuropathy group (*N*=150) [*n* (%)] |
|---|---|
| NSS | |
| Mild | 5 (3.3) |
| Moderate | 23 (15.3) |
| Sever | 122 (81.3) |
| MNSIa | |
| Abnormal | 150 (100.0) |

MNSIa, Michigan neuropathy screening instrument; N, number; NSS, neuropathy symptom score.

**Table 3 Objective scores among the neuropathy group**

| Objective scores | Neuropathy group (*N*=150) [*n* (%)] |
|---|---|
| NDS | |
| Mild | 33 (22.0) |
| Moderate | 105 (70.0) |
| Sever | 12 (8.0) |
| MNSIb | |
| Normal | 35 (23.3) |
| Abnormal | 115 (76.7) |

MNSIb, Michigan neuropathy screening instrument; NDS, neuropathy disability score.

HbA1C) was significantly elevated in the PN group compared with the other group (8.24 vs. 7.27% – *P*<0.001). Regarding NLR in our study, it was not significantly different between the two groups (*P*=0581). It had mean values of 2.17 and 2.1 in groups 1 and 2, respectively (Table 1).

NSS assessment revealed the presence of mild neuropathy in 3.3%, moderate neuropathy in 15.3%, and severe form in 81.3% of cases in the neuropathy cases. Regarding MNSIa assessment, it revealed abnormality in all neuropathy patients (100%) (Table 2). Regarding NDS in the current study, it revealed mild, moderate, and severe neuropathy in 22, 70, and 8% of cases, respectively. MNSIb revealed abnormality in 115 (76.7%) cases, and the remaining cases were normal (Table 3). TCSS showed the presence of mild, moderate, and severe neuropathy in 20, 73.3, and 6.7% of neuropathic cases, respectively. In addition, UENS had a mean value of 32.92 in the current study (Table 4).

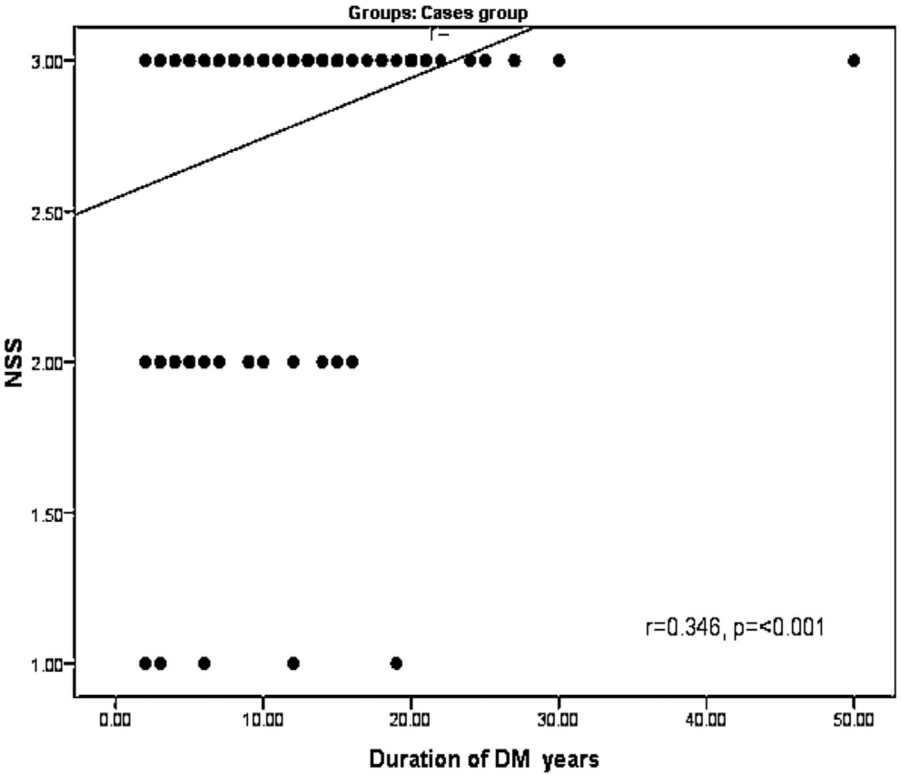
**Table 4 Subjective–objective scores among the neuropathy group**

| Subjective–objective scores | Neuropathy group (*n*=150) [*n* (%)] |
|---|---|
| TCSS | |
| Mild | 30 (20) |
| Moderate | 110 (73.3) |
| Sever | 10 (6.7) |
| UENS | |
| Mean±SD | 32.92±3.56 |

TCSS, Toronto clinical scoring system; UENS, Utah early neuropathy scale.

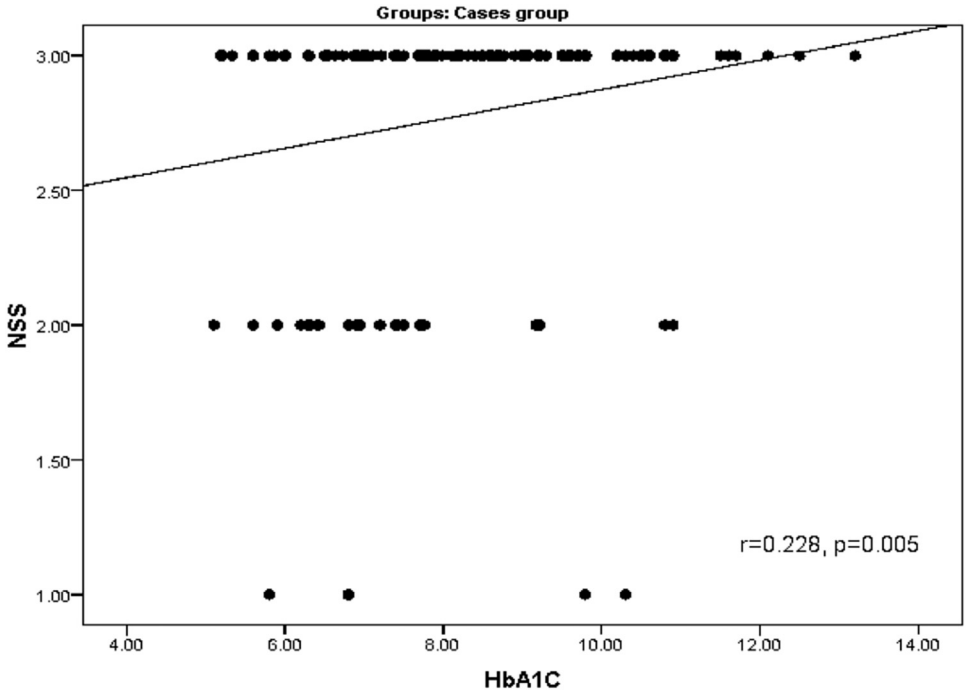
NSS showed a significant positive correlation with duration of diabetes, HbA1C, and the UENS ($P<0.05$) (Figs 1–3). Regarding NDS, it showed a significant positive correlation with MNSIb, HbA1C, TCSS, UENS, and the duration of diabetes ($P<0.05$). MNSIb showed a significant positive correlation with

**Figure 1**



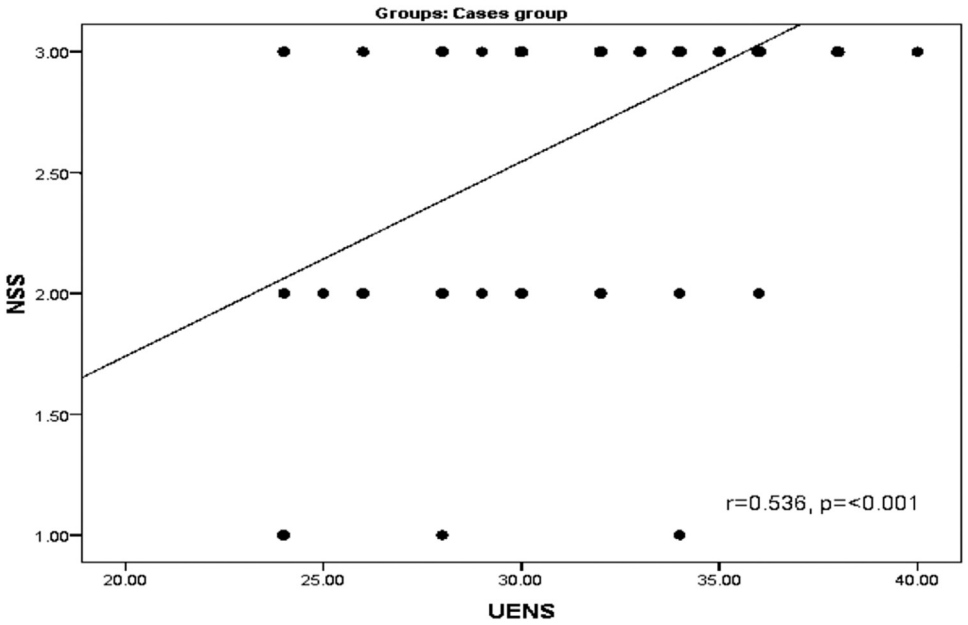

Scatter diagram for positive correlation between NSS and duration of DM. DM, diabetes mellitus; NSS, neuropathy symptom score.

**Figure 2**




Scatter diagram for positive correlation between NSS and HbA1C. HbA1C, glycated hemoglobin; NSS, neuropathy symptom score.

**Figure 3**




Scatter diagram for positive correlation between NSS and UENS. NSS, neuropathy symptom score; UENS, Utah early neuropathy scale.

**Table 5 Correlation between objective scores (neuropathy disability score, Michigan neuropathy screening instrument b) and other variables**

| Variables | NDS | | MNSIb | |
|---|---|---|---|---|
| | *r* | *P* | *r* | *P* |
| MNSIb | 0.646 | ≤0.001* | – | – |
| HbA1C | 0.180 | 0.028* | 0.218 | 0.007* |
| NLR | –0.060 | 0.467 | –0.102 | 0.216 |
| TCSS | 0.679 | ≤0.001* | 0.824 | ≤0.001* |
| UENS | 0.509 | ≤0.001* | 0.534 | ≤0.001* |
| Duration of DM | 0.399 | ≤0.001* | 0.398 | ≤0.001* |

DM, diabetes mellitus; HbA1C, glycated hemoglobin; MNSIb, Michigan neuropathy screening instrument; NDS, neuropathy disability score; NLR, neutrophil/lymphocyte ratio; TCSS, Toronto clinical scoring system; UENS, Utah early neuropathy scale. *Means highly significant.

**Table 6 Correlation between subjective–objective scores and other variables**

| Variables | TCSS | | UENS | |
|---|---|---|---|---|
| | *r* | *P* | *r* | *P* |
| NDS | 0.646 | ≤0.001* | 0.509 | ≤0.001* |
| NSS | 0.649 | ≤0.001* | 0.536 | ≤0.001* |
| MNSIb | 0.824 | ≤0.001* | 0.534 | ≤0.001* |
| HbA1C | 0.200 | 0.015* | 0.194 | 0.018* |
| NLR | –0.008 | 0.926 | –0.103 | 0.208 |
| TCNS | – | – | 0.596 | ≤0.001* |
| Duration of DM | 0.438 | ≤0.001* | 0.334 | ≤0.001* |

DM, diabetes mellitus; HbA1C, glycated hemoglobin; MNSIb, Michigan neuropathy screening instrument; NDS, neuropathy disability score; NLR, neutrophil/lymphocyte ratio; NSS, neuropathy symptom score; TCSS, Toronto clinical scoring system; UENS, Utah early neuropathy scale. *Means highly significant.

HbA1C, TCNS, UENS, and diabetes duration ($P<0.05$) (Table 5). TCSS had a significant positive correlation with NDS, NSS, MNSIb, HbA1C, and diabetes duration ($P<0.05$), whereas UENS had a significant positive correlation with NDS, NSS, MNSIb, HbA1C, TCSS, and diabetes duration ($P<0.05$) (Table 6).

With a cutoff value of 6.835%, HbA1C had a sensitivity and specificity of 80.5 and 54%, respectively, for identifying PN, with a diagnostic accuracy of 73.9%.

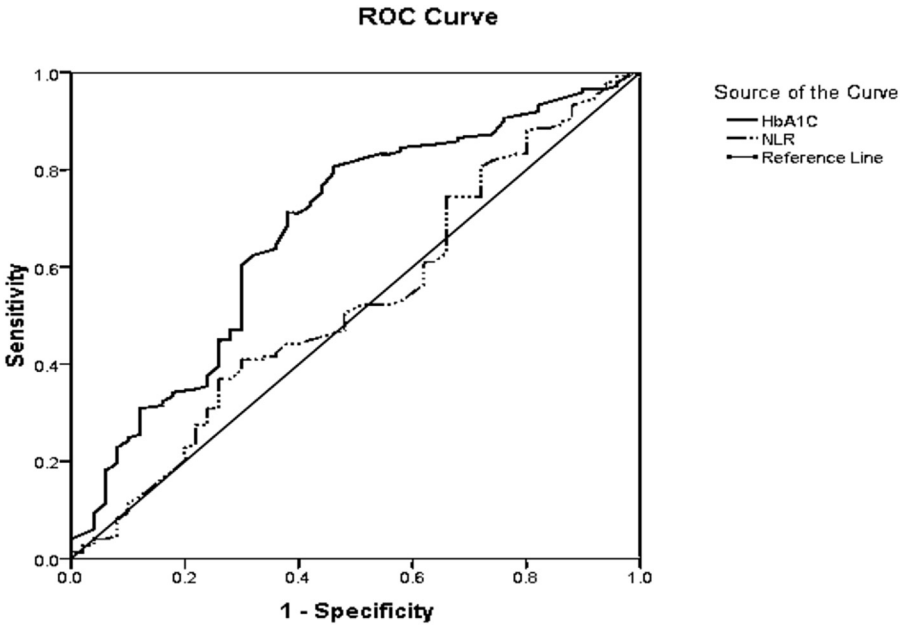
Regarding NLR, using a cutoff value of 2.15, it had a sensitivity and specificity of 50.3 and 52%, respectively, with a diagnostic accuracy of 50.5% (Fig. 4).

The duration of diabetes was significantly longer in cases with severe neuropathy based on NDS. Likewise, HbA1C showed the same changes ($P<0.05$) (Table 7). Similar to NDS, both HbA1C and duration of diabetes showed a significant elevation in cases with severe neuropathy according to NSS ($P<0.05$) (Table 8), whereas cases with severe neuropathy on TCSS showed significant elevation of HbA1C, along with significant prolonged duration of diabetes ($P<0.05$) (Table 9).

## Discussion

DPN is one of the commonest chronic complications of DM. It was documented that 26.4% of the cases experiencing T2DM have painful DPN, whereas about

**Figure 4**




Diagnostic accuracy of HbA1C and NLR in prediction of diabetic neuropathy. HbA1C, glycated hemoglobin; NLR, neutrophil/lymphocyte ratio.

**Table 7 Relation between duration of diabetes mellitus, glycated hemoglobin and neuropathy disability score**

| Variables | NDS | | | Test of significance | *P* value |
|---|---|---|---|---|---|
| | Mild | Moderate | Sever | | |
| Duration of DM | 5 (2–19) [ab] | 12 (2–27) [ac] | 16.5 (7–50) [bc] | KW=23.7 | <0.001* |
| HbA1C | 7.59±1.61[a]b | 8.34±1.57 [a] | 9.18±2.1 [a]b | *F*=4.84 | 0.009* |

DM, diabetes mellitus; *F*, analysis of variance test; HbA1C, glycated hemoglobin; KW, Kruskal–Wallis test; NDS, neuropathy disability score. [abc]Similar letters indicate significant difference between groups. *Means highly significant.

**Table 8 Relation between duration of diabetes mellitus, glycated hemoglobin and neuropathy symptom score**

| Variables | NSS | | | Test of significance | *P* value |
|---|---|---|---|---|---|
| | Mild | Moderate | Sever | | |
| Duration of DM | 6.00 (2–19)[a] | 5.00 (2–16) [b] | 12 (2–50) [ab] | KW=18.4 | <0.001* |
| HbA1C | 7.89±2.01 | 7.91±1.52 | 8.32±1.65 | *F*=6.13 | 0.002* |

DM, diabetes mellitus; *F*, analysis of variance test; HbA1C, glycated hemoglobin; KW, Kruskal–Wallis test; NSS, neuropathy symptom score. [abc]Similar letters indicate significant difference between groups. *Means highly significant.

**Table 9 Relation between duration of diabetes mellitus, glycated hemoglobin and TCNS**

| Variables | TCSS | | | Test of significance | *P* value |
|---|---|---|---|---|---|
| | Mild | Moderate | Sever | | |
| Duration of DM | 5.5 (2–19) [ab] | 12 (2–27) [ac] | 19 (10–50) [bc] | KW=28.6 | <0.001* |
| HbA1C | 7.41±1.52 [ab] | 8.42±1.56 [a] | 8.87±2.45[b] | *F*=5.36 | 0.006* |

DM, diabetes mellitus; *F*, analysis of variance test; HbA1C, glycated hemoglobin; KW, Kruskal–Wallis test; TCSS, Toronto clinical scoring system. [abc]Similar letters indicate significant difference between groups. *Means highly significant.

half of the DPN cases may not have any symptoms [11]. DPN mostly has a gradual course, and the severity of its pathologic alterations is mostly not consistent with the symptom appearance and severity. The typical manifestation is neuropathic pain (a feeling of burning, tingling electric, shooting, and sharp pain) [12], and consequently, ulceration of foot and its amputations may take place [13].

Although neurophysiologic studies represent an objective and sensitive tool in the diagnosis of diabetic neuropathy, they remain limited by the availability of equipment, expert physicians, and trained technicians, in addition to cost, inconvenience to patients, and pain. These limitations are more evident when used as a follow-up tool or screening tool in an outpatient setting. There is thus a need to develop simpler tools

that can bridge this gap, hence the development of neuropathy scores [14].

We included 200 cases with T2DM who were divided into two groups: group 1 included 150 diabetic cases with painful peripheral diabetic neuropathy, and group 2 included 50 diabetic cases without neuropathy.

In our study, there was a significant difference between the study groups in accordance with duration of DM. It was majorly longer in the PN group (median 11 vs. 6 years in non-neuropathy group).

The duration of DM is a well-known major risk factor for diabetic neuropathy [15,16]. In both T1DM and T2DM, the neuropathy association with the duration of DM is independent of patients' age [17,18]. This strong association was obviously documented in many studies [19–21].

In the current study, there was no significant difference between the two groups regarding the prevalence of obesity ($P$=0.935). Obese individuals represented 49.3 and 50% of cases in groups 1 and 2, respectively. This comes in agreement with Khawaja *et al.* [22], who reported no significant difference regarding BMI of the included cases ($P$=0.052). Obesity was present in 57.6 and 42.4% of cases in groups 1 and 2, respectively.

Regarding HTN in the current study, it was significantly more prevalent in the neuropathy group (75.3 vs. 48% of cases in the other group – $P$<0.001). HTN is another risk factor for diabetic neuropathy [23], but there seems to be a difference between the T1DM and T2DM [17]. In TIDM, the data are confirmatory [23,24]. HTN has been recognized as the most powerful predictor of diabetic neuropathy, as it elevated the relative risk about four times in 6 years [24]. Correspondingly, it has been documented that systolic HTN was an independent predictor subsequent to adjustment for age, duration of diabetes, and glycemic control [23]. On the contrary, studies in T2DM have been inconclusive [25,26]. Of note, tight control of blood pressure in the United Kingdom Prospective Diabetes Study did not decrease the neuropathy deterioration [27].

In our study, HbA1C was significantly elevated in the PN group in comparison with the other group (8.24 vs. 7.27% – $P$<0.001). With a cutoff value of 6.835%, it had a sensitivity and specificity of 80.5 and 54%, respectively, for identifying PN, with a diagnostic accuracy of 73.9%.

HbA1C as a risk factor for DPN has been established by a number of studies [28,29]. In accordance with research, cases having T2DM and HbA1C more than 7.0% exhibited an increased risk of DPN, demonstrating a linear relationship [29]. In another meta-analysis, it was suggested that the early control of levels of HbA1C can significantly decrease the possibility of DPN development [30]. Conversely, another study reported that HbA1C was significantly elevated in the non-neuropathy group compared with the neuropathy cases (8 vs. 7.1% in groups 1 and 2, respectively – $P$<0.001) [22]. Furthermore, another study reported no significant difference regarding HbA1C levels in diabetic cases with PN and the other group (8.8 vs. 8.6% in groups 1 and 2, respectively – $P$=0.3) [31]. This heterogenicity in results could be explained by the fact that intensive control of blood glucose levels significantly decreased the development of clinical neuropathy, and the advantages of previous intensive control of blood glucose levels for neuropathy were maintained in cases with T1DM [32], whereas in T2DM, this outcome was found less conclusive [33,34].

Regarding NLR in our study, it did not have a significant difference between the two groups ($P$=0581). This came in contrast with Xu *et al.* [11], who reported that the mean neutrophil level in the diabetic without neuropathy was 3.80±1.23, whereas in the group with neuropathy, the level was higher at 4.04±1.05, with significant difference between the two groups. In addition, they reported that the mean lymphocyte level was 1.84±0.75 in the diabetic without neuropathy, and in the group with neuropathy, the level was 1.61±0.47, with highly significant difference between the two groups [11]. The difference between the two results may be owing to factors influencing the variation of NLR like inherent factors such as age, sex, and genetic constitution, environmental factors such as season, and lifestyle factors such as smoking and diet [35].

NSS assessment showed a significant positive correlation with NDS, MNSIb, HbA1C, TCSS, UENS, and the duration of diabetes ($P$<0.05). In cases with DM, correlations between different tests and scores of neuropathy were documented [36]. An association between NDS and NSS was noted [37], as between both NDS and NSS and number of individual variables of nerve conduction studies [37,38].

NDS had a significant positive correlation with MNSIb, HbA1C, TCSS, UENS, and the duration of diabetes ($P$<0.05). NDS is a widely used clinical score with a high predictive value and reproducibility

[39]. It has been shown to be significantly associated with neuropathological changes in peripheral nerves [37] and significantly correlated to nerve conduction study [40]. It has also been proven to be the most reliable neurological test for detecting and grading DPN [41]. In a previous study, NDS had a sensitivity and specificity of 89 and 100%, respectively, for identifying DPN using a cutoff value of 4 [9].In the current study, UENS had a significant positive correlation with NDS, NSS, MNSIb, HbA1C, and diabetes duration ($P<0.05$). The UENS was planned to reveal the initial small-fiber sensory neuropathy and identify small sensory alterations. It spotlights on the examination of distal loss of sensation and involves minimal examination of muscle and reflex, examining only the strength of extensor hallucis longus muscle and ankle reflexes [42]. In a previous study, UENS had a sensitivity and specificity of 85 and 97%, respectively, for identifying DPN, using a cutoff value of 3 [9].

All in all, all tests used in the current study showed significant correlation not only with each other but also with other confirmed risk factors for diabetic neuropathy like prolonged duration and elevated HbA1C. This only means that all of these scores showed the same changes according to the severity of neuropathy.

Generally, most clinical neuropathy scores are noninvasive, inexpensive, sensitive-specific, and highly predictive of clinical end points. Furthermore, combining multiple scores has been shown to be better than using a single test [41].

This study has some limitations; first of all, it is a single-center study. Therefore, more studies from different centers should be conducted. Moreover, more cases should have been included.

## Conclusion

High grades of the scores performed in this study were associated with a severe form of neuropathy. Both duration of diabetes and HbA1C levels had a significant positive correlation with these scores. Regarding neutrophil/lymphocytic ratio in our study, it did not have a significant difference between the two groups.

### Acknowledgements

Authors' contributions: M.A.: data collection from case group and control group and shared in writing. M.M.: responsible for the laboratory part of the research (TSH, leptin, and TPO) and shared in writing and data interpretation. N.A.E.: shared in writing, share in clinical part of the research, in statistical analysis, and data reviewing and interpretation. She is our main supervisor of the work. R.B.: gave the idea of the work, shared in writing (main role), shared in clinical part and follow-up of patients, was responsible for statistical analysis, and participated in data reviewing and interpretation.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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