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Review of various scoring systems for screening of chronic sensorimotor peripheral neuropathy in Type II Diabetes Mellitus

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ABSTRACT
Diabetic peripheral neuropathy (DPN) is one of the most common microvascular complications in type 2 diabetes mellitus. Nerve conduction study (NCS) has long been a minimal criterion or a gold standard test for confirming the diagnosis of peripheral neuropathies. Potential disadvantages of NCS are limited availability for routine diagnostic evaluation of DPN and insensitive for the identification of small-fibre neuropathy. Many diagnostic tests have been designed to screen and diagnose peripheral neuropathy in individuals with diabetes, but there exists a disagreement as to which is the most appropriate and reliable clinical neuropathy scale for peripheral neuropathy in patients with diabetes.This narrative review aims to summarise the existing knowledge of different scoring systems with respect to NCS for screening of chronic sensorimotor diabetic peripheral neuropathy in type 2 diabetics.

1. INTRODUCTION
Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both[1]. Diabetic peripheral neuropathy (DPN) is one of the most common microvascular complications in both type1 and type 2 diabetes. 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 is the most common component in the causal sequence to foot ulceration[2].
Microangiopathy lesion is featured by several biochemical and structural changes in the microvasculature that lead to extracellular matrix protein synthesis and thickening of capillary basement membrane. These changes are developed as consequences of increased glycation end products, oxidative stress, low grade inflammation and neovascularization of the vasa vasorum which are directly related to micro and macrovascular complications. Therefore, patients are prone to long – term damage and failure of various organ systems leading to retinopathy, neuropathy, nephropathy, coronary artery disease and stroke. The risk is directly proportional to both the duration and magnitude of hyperglycemia[3].
Early screening for symptoms and signs of diabetic neuropathy is important, since it creates a chance to detect the neuropathy at its earliest asymptomatic stages and thus prevent further progression[4]. The Nerve Conduction Study (NCS) enables sensory and motor abnormalities associated with neuropathy to be diagnosed even if the dysfunction is subclinical[5]. There is increasing concern regarding diabetic neuropathy complications as these are considered a leading cause of disability due to foot ulceration and amputation, gait disturbances and injuries secondary to falls. Such complications severely lower the quality of life in patients and increases health cost associated with diabetes[5].
Numerous clinical scoring systems have been compiled to evaluate light touch, pin-prick, vibration, proprioception, muscle strength and ankle reflexes. Many clinical scoring systems have been designed to screen and diagnose peripheral neuropathy in individuals with diabetes, but to the best of our knowledge, there is no appropriate and reliable clinical neuropathy scale for peripheral neuropathy.

Research Question
Is there any reliable and valid clinical neuropathy scale which is the most appropriate scoring system to screen for DPN instead of NCS for clinical diagnosis of DPN ??

2. RESULTS

Clinical Diagnosis of Diabetic Polyneuropathy with the Diabetic Neuropathy Symptom and Diabetic Neuropathy Examination Scores by **Jan-Willem G. Meijer, MD et al**[6] evaluated the discriminative power of the Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scores for diagnosing diabetic polyneuropathy (PNP), as well as their relation with cardiovascular autonomic function testing (cAFT) and electro-diagnostic studies (EDS). They concluded the DNS and DNE scores are able to discriminate between patients with and without PNP and are strongly related to cAFT and EDS.

Major risk factors for the diabetic foot complications is distal symmetric sensorimotor polyneuropathy (PNP)[7]. San Antonio consensus panel has recommended that at least one measurement should be performed in five different diagnostic categories[8].

These are :

- symptom scoring
- physical examination scoring
- quantitative sensory testing (QST)
- cardiovascular autonomic function testing (cAFT)
- electro-diagnostic studies (EDS)

Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scores were developed because none of the above fulfilled the methodological criteria for diagnostic tests[6]. The construct validity of DNS guidelines was studied in relation to QST because of their predictive value to the development of diabetic foot complications[9].

The DNS score is a four-item validated symptom score with high predictive value to screen for PNP in diabetes[10]. Symptoms screened in DNS are:

a) unsteadiness in walking
b) neuropathic pain
c) paraesthesia
d) numbness.

The presence of one symptom is scored as 1 point, the maximum score is 4 points. A score of 1 or higher is defined as positive for PNP.

The DNE score is validated score[6].

The score contains eight items -

a) muscle strength (2 items)
b) reflexes (1 item)
c) five concerning sensation (five items).

Each item is scored from 0 to 2

0 - normal and

2 - severely disturbed

The maximum score is 16 points.

A score of >3 points is defined as positive for PNP.

cAFT

HRV analysed after discrete Fourier transformation of systolic blood pressure and R-R interval length measurement. Using Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[11] BRS was determined by the transfer function method. A BRS <3 ms/mmHg was considered indicative for cardiovascular autonomic neuropathy[12,13]. The prognostic value for BRS in DM is not clear. Since no reference values of HRV are available, the median of the control group 9.2 ln (ms^2) was used.

Electro-diagnostic testing (EDS)

As parameters, the mean invasive MFCV and the fastest/slowest ratio (F/S ratio) representing the scatter of conduction velocities were used and compared with normative values.

Neuropathy Sum score

An overall score was composed of

a) DNS score (symptom score)
b) DNE score (examination score)
c) BRS (cAFT)
d) NCS (EDS)
e) Semmes Weinstein monofilament testing (QST)

For each abnormal test result 1 point was given, the maximum score was 5 points.

In conclusion, the study showed that the Neuropathy Sum score based on the five diagnostic categories as advised by the San Antonio consensus[8], also shows high incidences even in the control group with abnormal test results, leading to a risk of overdiagnosis. Further research should be done to characterize an optimal set of diagnostic categories for diabetic PNP.

DNS and DNE scores allow discrimination between patients with and without diabetic PNP and can be used for clinical diagnosis of Diabetic PNP.

In a study conducted by **Fehmeda Farrukh Khan et al**[14] comparing performance of two different clinical scoring systems in diagnosing distal sensory polyneuropathy in patients with T2DM concluded that DNE score alone and in combination with DNS score is reliable in predicting DSPN(Distal symmetrical polyneuropathy) and is more specific than DNS score in evaluating DSPN.

Study done by **Amreen Asad et al**[15] titled reliability of neurological scores for assessment of sensorimotor neuropathy in T2DM compared the reliability of commonly used neurological scoring systems taking the nerve conduction studies as the gold standard and concluded that combining different scores like Diabetic Neuropathy Symptom Score (DNS), modified Neuropathy Symptom Score (NSS), Diabetic Neuropathy Examination (DNE) and modified Neuropathy Disability Score (NDS) gives better sensitivity and specificity. NDS is the most reliable neurological test for detecting and grading DPN.

J W Meijer et al[16] conducted study with total of 73 patients with diabetes, examined the Neuropathy disability score (NDS). Monofilaments and biothesiometry were used as clinical standards for PNP to modify the NDS. They concluded that DNE is a sensitive and well-validated hierarchical scoring system that is fast and easy to perform in clinical practice.

E L Feldmanb et al[17] conducted study with 56 outpatients with confirmed type 1 or 2 diabetes were administered the standardized quantitative components required to diagnose and stage diabetic neuropathy according to the San Antonio Consensus Statement and the Mayo Clinic protocol. These same patients were then assessed with the MNSI (Michigan Neuropathy screening instrument) and the MDNS (Michigan Diabetic neuropathy score)The results indicated that the MNSI is a good screening tool for diabetic neuropathy and that the MDNS coupled with nerve conduction provides a simple means to confirm this diagnosis.

J C Won[18] et al conducted a study in which questionnaires and medical records were used to collect data on 4000 patients with Type 2 diabetes from the diabetes clinics of 40 hospitals throughout Korea. Diabetic peripheral neuropathy was diagnosed based on a review of medical records or using the Michigan Neuropathy Screening Instrument score and monofilament test. They found that there was a high prevalence of peripheral neuropathy in patients with Type 2 diabetes in Korea and those patients were far more likely to have complications or co-morbidities

Mark Davies et al[19] conducted a cross-sectional descriptive study consisting of two phases: phase 1, a postal survey to patients with type 2 diabetes (an initial screening questionnaire including one question about pain); phase 2, neurological history and examination using the Toronto Clinical Scoring System. Subjects with pDPN (Painful diabetic peripheral neuropathy) or mixed (pDPN and nonneuropathic) pain completed the Neuropathic Pain Scale. This study showed a prevalence of pDPN of 26.4%.

Edward J Bastyr 3rd et al[20] used the (Neuropathy total symptom score)NTSS - 6 questionnaire was to evaluate the frequency and intensity of individual neuropathy sensory symptoms identified frequently by patients with DPN (ie, numbness and/or insensitivity; prickling and/or tingling sensation; burning sensation; aching pain and/or tightness; sharp, shooting, lancinating pain; and allodynia and/or hyperalgesia). The NTSS-6 was administered 8 times over a 1-year period to DPN patients. They concluded that NTSS-6 provided a valid assessment of neuropathy sensory symptoms in this sample of patients with DM and DPN, which suggests that it may be useful for symptom evaluation in clinical trials and practice

Vera Bril[21] et al conducted study on eighty-nine patients with both type 1 and type 2 diabetes, ascertained from a large therapeutic randomized controlled trial, were included in this cross-sectional, observational cohort study. Morphological severity of DSP was expressed as the FD (fiber density) in the sural nerve biopsy. The Toronto CSS (Clinical Scoring System) was applied to all patients to determine a clinical neuropathy score. General linear regression models were used to assess the relationship between the morphological severity of DSP and the Toronto CSS. The Toronto CSS is a valid instrument to reflect the presence and severity of DSP as measured by sural nerve morphology and electrophysiology

D R Cornblath et al[22] measured the inter- and intrarater reliability of the Total Neuropathy Score (TNS) and preformed a cross-sectional validation study of the TNS and its subscales with the Mayo Clinic measures of neuropathy, neuropathy symptom score (NSS), and the neurologic impairment score (NIS) in five They concluded that total neuropathy score is a validated measure of peripheral nerve function and could be used as an end point for clinical trials of peripheral neuropathy.

Yi-Ching Weng et al[23] conducted cross-sectional study with aim at determining the prevalence of distal symmetrical polyneuropathy (DSPN) and diabetic peripheral neuropathic pain (DPNP) in participants with type 2 diabetes mellitus (T2DM); finding the risk factors for DSPN and DPNP via biochemical tests; and correlating DSPN and DPNP with the results of electrophysiologic studies, quantitative sensory tests, and neurologic examination. They concluded that a modified semiquantitative vibration thermal threshold test combined with nerve conduction tests could identify most of the patients with DSPN, subclinical DSPN, and minimal DSPN.

Zhen-Fei Li et al[24] conducted a study with the aim to evaluate the diagnostic efficacy of different tendon reflexes in detecting diabetic peripheral neuropathy (DPN) and concluded that assessment of tendon reflexes can be proposed as a test for screening diabetic polyneuropathy.

Labani M. Ghosh et al[25] aimed to evaluate the reliability of the Diabetic Neuropathy Examination Score (DNE), 10-g Semmes-Weinstein Monofilament Examination and Quantitative Sensory Testing by Vibration Perception Threshold (VPT) in the diagnosis of diabetic polyneuropathy to seek a cost effective and reliable screening method in diabetic OPD

and IPD against the gold standard of NCS. They concluded that there is correlation between the total neurological scores and NCV and it can be used to screen all diabetic patients for earliest signs of diabetic neuropathy with sustainable results.
Mudjiani Basuki et al[26] aimed to determine Toronto Clinical Neuropathy (TCN) and modified Toronto clinical neuropathy (mTCN) scores in distal diabetic sensorimotor polyneuropathy patients and concluded that TNC score above 4 could be used as a screening test, while score above 8 could be used as a diagnostic test for distal DSP.
A Chawla et al[27] planned to validate the neuropathy symptoms score (NSS) + neuropathy disability score (NDS) as per "Young et al" criterion in clinical diagnosis with the standard well validated screening method of measuring vibration perception threshold (VPT) with a biothesiometer in middle aged people with diabetes where foot care practices are scantly followed and concluded that neurological examination like NSS & NDS can be an important bed side tool in the clinics for early diagnosis of DPN with a sensitivity of 71.1% & specificity of 90%.

Research Gaps
Many diagnostic tests have been designed to screen and diagnose peripheral neuropathy in individuals with diabetes, but there exists a disagreement as to which is the most appropriate and reliable clinical neuropathy scale for peripheral neuropathy in patients with diabetes. To the best of our knowledge, no study has been conducted in India to find the most appropriate scale for diagnosing diabetic neuropathy. So the future scope of study can be to combine all the reliable and valid clinical neuropathy scales and calculate sensitivity and specificity of each score compared to nerve conduction study (NCS) as the gold standard. This research pursuit may help clinicians find the most appropriate scoring system which can be used to screen for DPN as a viable replacement of NCS for the clinical diagnosis of DPN.

3. CONCLUSION
DPN is one of the most common microvascular complications in type 2 diabetes mellitus. NCS has long been a minimal criterion or a gold standard test for confirming the diagnosis of peripheral neuropathies. However there are two potential disadvantages of NCS - NCS has limited availability for routine diagnostic evaluation of DPN and it is insensitive for the identification of small-fibre neuropathy.
Research leading to an early detection of DPN by replacing a complicated method (like NCS) with a cost effective simple scoring system will help in early diagnosis of DPN and hence prevent complications associated with it. The accuracy of the used scoring systems as replacement of NCS for screening or diagnosis of DPN will also supply more comprehensive evidence about peripheral neuropathies in diabetes mellitus type 2 .

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