

## Research



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## Clinical utility of the DN4 questionnaire in the assessment of neuropathic pain in patients with type 2 diabetes: experience from a newly created diabetes clinic in Cameroon

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## Abstract

**Introduction:** early diagnosis of peripheral neuropathy in people with diabetes mellitus is important. Screening tools are either expensive or cumbersome, and thus impractical in low-resource settings. The DN4 questionnaire is a simple alternative. We assessed the performance of the DN4 Questionnaire in detecting neuropathic pain associated with diabetic peripheral neuropathy in patients with type 2 diabetes. **Methods:** we included 58 adult patients with type 2 diabetes mellitus. The presence of neuropathy was diagnosed using medical history, physical examination, and a digital biothesiometer vibration perception threshold scores. A blinded investigator performed the DN4 interview. Those who had a DN4 score  $\geq 4$  were considered to have peripheral polyneuropathy. Student's *t*-test and the non-parametric equivalent were used to make comparisons where necessary. A *P*-value of less than 0.05 was considered statistically significant. **Results:** the DN4 Questionnaire diagnosed neuropathy in 33 (56.9%) of the 58 participants. It showed a high diagnostic accuracy for painful diabetic neuropathy with a positive predictive value (PPV) of 90%, and a negative predictive value of 70.0%. Its sensitivity and specificity was 67.4% and 66.7% respectively. **Conclusion:** the DN4 questionnaire may serve as an adequate tool in resource-limited settings given its simplistic and pragmatic approach. Healthcare providers would require adequate training for the administration of interview questions and extensive validation in a larger population of patients with type 2 diabetes in Cameroon is recommended.

## Introduction

Diabetic peripheral neuropathy is the most common microvascular complication of diabetes mellitus. A widely accepted definition of diabetic peripheral neuropathy is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes" [1]. Neuropathies severely

decrease patients' quality of life, as its sensory and motor symptoms can be very unpleasant. Also, unchecked neuropathy increases the risk of secondary complications such as foot ulcers, and eventual amputation, making early diagnosis very important [2]. Various models, scores and diagnostic kits are available to assess, diagnose and grade the severity of diabetic sensory neuropathy [3]. These include; the United Kingdom Screening Test, "douleur neuropathique en 4 questions", clinical stratification method using the Toronto Clinical Neuropathy Score, the Neuropathy Total Symptom Score (NTSS-6), the 10g Semmes-Weinstein Monofilament Test, Intra-epidermal nerve fiber analysis of skin biopsy, and nerve conduction studies. Although nerve conduction studies remain the most reliable, accurate and sensitive measure of peripheral nerve functions, vibration perception abnormalities have been shown to be the earliest finding in peripheral neuropathy [4]. Adequate nerve conduction and vibration perception studies are often not easy to perform in clinical settings because they are expensive and time-consuming. Simple screening tools such as the douleur neuropathique en 4 questions form (DN4 questionnaire) may therefore offer a simple, practical alternative especially in resource depleted settings. The DN4 Questionnaire is a screening tool for neuropathic pain consisting of 10 interview questions (DN4-interview) and physical tests which has been validated for the diagnosis of diabetic peripheral neuropathy in western populations [5]. We therefore aimed to assess the performance of the DN4 questionnaire in detecting neuropathic pain associated with diabetic peripheral neuropathy in patients with type 2 diabetes with lower limb painful symptoms, compared to the more accurate vibration perception threshold determined by a digital biothesiometer.

## Methods

**Design and setting:** this was a descriptive and analytic survey carried out at the newly-created diabetes clinic (diabetes and hypertension

treatment centre) of the Bafoussam Regional Clinic from June to December 2015. This diabetes clinic started in March 2013 as a community-hospital participatory effort. The Bafoussam Regional Hospital is a regional referral hospital that serves 22 district hospitals in the west region of Cameroon.

**Ethical consideration and confidentiality:** administrative authorization to conduct the survey was obtained from the Bafoussam Regional Hospital. All diabetes patients involved provided a written informed consent prior to the start of the survey. All patient data were collected with anonymized questionnaires.

**Study participants:** a total of 100 adult type 2 diabetes patients follow-up at the newly-created diabetes clinic were randomly selected from their medical records to participate in the survey. Fifty-eight (58) patients were finally included to undergo the survey based on complaints of paresthesia and pain at their lower limbs for a minimum period of 3 months prior to the survey date irrespective of gender. Figure 1 shows the flow diagram for the study.

**Data collection tools:** socio-demographic characteristics and medical history were recorded onto a pre-structured questionnaire. Biophysical characteristics were measured and recorded after a complete medical examination. The presence of neuropathic pain was assessed using the DN4 questionnaire. Fasting capillary glucose was measured using a glucose meter (Accu-Chek® Active, Roche, Germany).

**Assessment for neuropathic pain using the DN4 Questionnaire:** the DN4 questionnaire was used to screen for the presence of neuropathic pain. This questionnaire consisted of 4 sections; 3 sections concerned with symptoms review and associated symptoms and the 4<sup>th</sup> section reserved for physical examination. DN4-interview questions included burning, painful cold, electric shocks, tingling, pins and needles, numbness and itching. Examination of the patient included hypoesthesia to touch, hypoesthesia to prick, and brushing. This was

evaluated using the *owen mumford*® *Neuropen*. Each item was scored “yes” or “no.” Total questions across the 4 sections summed up to 10, with “yes” answer scored as 1, and “no” as 0. Neuropathic pain was diagnosed if the total DN4 score was greater than or equal to 4 [5].

**Assessment of vibration perception threshold (VPT):** a single investigator (blinded to the DN4 Questionnaire) used a digital biothesiometer (*VibroSense*®- Genesis Medical Systems Pvt. Ltd, Telangana, India) to measure the vibration perception threshold (VPT) following a standardized procedure. The vibrating Biothesiometer probe was applied at an angle perpendicular to the testing site. The VPT was the average of 6 point measurement at the plantar surface of the big toe, 1<sup>st</sup> metatarsal, 3<sup>rd</sup> metatarsal, and 5<sup>th</sup> metatarsal, instep, and heel. Once the probe was placed on the testing site, the voltage was slowly increased at the rate of 1 mV/sec and the VPT value was defined as the voltage level when the patient indicated that he/she felt the vibration. This was measured in both feet and the highest score was noted as the VPT for that particular patient. VPT was graded as Normal  $\leq 15$  V, Grade I: 16-25 V, and Grade II  $> 25$  V [6].

**Statistical analysis:** all data recorded onto the pre-structured questionnaires were entered into Microsoft Excel 2010 spreadsheet. All entries on computer were further checked against that on paper item by item to ensure accuracy. Data set was later exported to IBM SPSS 23.0 for analysis. Results were presented as frequencies or mean and standard deviation. The student's t-test and the non-parametric equivalent were used to make comparisons where necessary. A p value of less than 0.05 was considered statistically significant for all analyses.

## Results

**Socio-demographic characteristics of the study population:** of the 58 diabetes patients screened for neuropathic pain, 31 (54.5%) were males. The mean age of the study population was  $62.1 \pm 9.9$

years, with a median duration of diabetes of 3.5 (1.0-11.5) years and a median fasting blood glucose of 130 (94.0-168.5) mg/dl. The mean weight of the participants was  $80.1 \pm 18.1$  kg with a mean body mass index (BMI) of  $29.1 \pm 5.8$  kg/m<sup>2</sup>. Overall 35 (60%) participants had hypertension with 54 subjects having a positive psycho-stimulant (alcohol and tobacco) consumption history as shown in Table 1.

**Assessment of diabetic peripheral neuropathy based on vibration perception threshold:** fifty-two (52) participants underwent the assessment for vibration perception threshold. A total of 43 people had neuropathy according to VPT findings. The mean VPT score was higher in patients with DN4 score  $\geq 4$  compared to those with VPT score  $< 4$ ;  $21.7 \pm 9.0V$  vs.  $26.3 \pm 10.2V$ ,  $p=0.108$  (Table 2)

**Frequency of neuropathic pain and the diagnostic accuracy of the DN4 Questionnaire:** neuropathic pain was determined in 33 (56.9%) of the 58 participants with a DN4 score  $\geq 4$ . Patients with DN4 score  $\geq 4$  were older than those with DN4  $< 4$ ,  $63.8 \pm 9.5$  years vs  $59.8 \pm 10.3$  years,  $p=0.125$ . Table 3 shows the characteristics of the study participants with regard to their DN4 scores. The sensitivity and specificity of the DN4 was 67.4% and 66.7% respectively with a positive predictive value (PPV) of 90%, and a negative predictive value of 70.0%.

## Discussion

We aimed to investigate the performance of the DN4 Questionnaire in assessing neuropathic pain in patients with type 2 diabetes with peripheral neuropathy diagnosed by vibration perception thresholds. We found that 56.9% of our study participants had neuropathic pain by the DN4 Questionnaire. The DN4 questionnaire however had a low sensitivity and specificity but with a high positive predictive value. Its high positive predictive value is comforting to the clinician as it suggests that a positive diagnosis reliably points to the presence of neuropathy. The PPV of 90.6% is high, and comparable to the findings of Timmerman [7]. The sensitivity of the DN4 found in our study was

64.7%. This is lower than the 79.8% found by Perez in Spain [8] and can be explained by the low duration of diabetes in our study population with a median duration of just 3.5 years. The development of microvascular complications in diabetes increases exponentially with increasing duration of diabetes [9]. As such, the low sensitivity found here is not alarming, when compared to their duration of diabetes. Also worth noting that 43% of our study population attained primary education only. This might have influenced the sensitivity of the DN4 interview questions, as participant intellect and comprehension of the questions asked is an important factor in boosting accuracy. This study however has some limitations. The small sample size may have affected the overall power to show a difference between the DN4 score categories. This also did not allow us to examine for characteristics associated with neuropathic pain as other studies have reported [10]. Nevertheless, this is one of the first studies investigating the performance of a simple tool such as the DN4 Questionnaire in assessing neuropathic pain in a diabetic population in sub-Saharan Africa. Both the administration of the DN4 Questionnaire and the use of the digital biothesiometer require appropriate training which may booster the performance of such tools. Also, as peripheral neuropathy is a progressive continuum of symptoms, with vibration abnormalities first, followed by pain and other sensory abnormalities, lack of electromyography meant that accurate diagnosis of peripheral neuropathy type/stage was impossible. As such, the DN4 questionnaire would have missed early neuropathy cases not yet manifesting as pain which in some cases may have been picked by the vibration perception threshold.

## Conclusion

The DN4 questionnaire showed low sensitivity and specificity but with a high positive predictive value in identifying diabetic peripheral neuropathy. Therefore, the DN4 questionnaire may serve as an adequate tool in resource-limited settings given its simplistic and pragmatic approach, but would need

adequate training in the administration of the interview questions and extensive validation in a larger population of patients with type 2 diabetes.

#### *What is known about this topic*

- *Diabetic peripheral neuropathy is the most common microvascular complication of diabetes mellitus;*
- *Nerve conduction studies remain the most reliable, accurate and sensitive measure of peripheral nerve functions, though quite challenging to perform in clinical settings;*
- *The DN4 Questionnaire is a screening tool for neuropathic pain associated to diabetic peripheral neuropathy but has not been validated in sub-Saharan Africa.*

#### *What this study adds*

- *This study provides preliminary data on the validation of the DN4 Questionnaire in the assessment of neuropathic pain associated with diabetic neuropathy in a sub-Saharan African population;*
- *DN4 Questionnaire has a low sensitivity and specificity but a high positive predictive value in the assessment of peripheral neuropathy in a population of type 2 diabetes patients in Cameroon;*
- *Adequate training in the administration of the interview questions and an extensive validation study in a larger number of patients with type 2 diabetes may be necessary.*

## Competing interests

The authors declare no competing interests.

## Authors' contributions

JCK, designed and collected the data for the study. DT and JCK performed the statistical analysis. BBA, DT, AOB, and JCK wrote and reviewed the manuscript. All authors read and approved the final manuscript.

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## Tables and figure

**Table 1:** general characteristics of the study population

**Table 2:** categories by assessment of DN4 questionnaire

**Table 3:** diagnostic accuracy of DN4 questionnaire score compared to VPT

**Figure 1:** flow diagram of participant recruitment in the study

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**Table 1:** general characteristics of the study population

Characteristics	Total N=58	Male N=31	Female N=27
Age, years (mean ± SD)	62 ± 9.9	64.6 ± 9.3	59.3 ± 10.1
Residence setting			
Urban	55	29	26
Rural	3	2	1
Level of education			
None/Primary	25	6 (24.0)	19 (76.0)
Secondary or more	33	25 (72.8)	8 (24.2)
Hypertension (Yes)	35	23	12
Duration of diabetes, years (median, IQR)	3.5 [1.0-11.5]	5.5 [1.0-14.3]	3.0 [1.0-9.0]
Smoking (Yes)	8	7 (87.5)	1 (12.5)
Alcohol consumption (Yes)	46	26 (56.5)	20 (43.5)
SBP, mmHg (mean ± SD)	145 ± 24.5	152.3 ± 24.6	137.5 ± 22.2
DBP, mmHg (mean ± SD)	90.6 ± 18.5	94.1 ± 20.4	86.6 ± 15.4
Weight, kg (mean ± SD)	80.1 ± 18.1	81.7 ± 14.9	78.2 ± 21.3
BMI, kg/m <sup>2</sup> (mean ± SD)	29.1 ± 5.8	27.3 ± 4.3	31.7 ± 6.7
Fasting glycemia, mg/dl (median, IQR)	130 [94.0-168.5]	128.0 [85.0-167.0]	139.0 [110.8-183.3]

IQR, Interquartile range. SD, Standard deviation

**Table 2:** table showing categories by assessment of DN4 questionnaire

Characteristics	Group 1 (n=25) DN4 < 4	Group 2 (n=33) DN4 ≥4	P-value
Age, years (mean ± SD)	59.8 ± 10.3	63.8 ± 9.5	0.125
Gender			
Male (%)	10 (32.3)	21 (67.7)	0.074
Female (%)	15 (55.6)	12 (44.4)	
Hypertension (Yes)	16 (45.7)	19 (54.3)	
Duration of diabetes, years (median, IQR)	3.0 [1.0 ± 8.3]	6.0 [1.0 ± 14.8]	0.157
Smoking (Yes)	1 (12.5)	7 (87.5)	0.125
Alcohol consumption (Yes)	19	26	
SBP, mmHg (mean ± SD)	146.2 ± 25.7	144.8 ± 23.9	0.838
DBP, mmHg (mean ± SD)	90.8 ± 19.2	90.5 ± 18.2	0.938
Weight, kg (mean ± SD)	77.4 ± 15.4	82.1 ± 19.9	0.328
BMI, kg/m <sup>2</sup> (mean ± SD)	29.1 ± 4.5	29.1 ± 6.7	0.975
Fasting glycemia, mg/dl (median, IQR)	135.0 [108.5 ± 176.0]	130.0 [85.0 ± 166.0]	0.445
Vibration Perception Threshold			
VPT, V (mean ± SD)	21.7 ± 9.0	26.3 ± 10.2	0.108
<15 V	6 (66.7)	3 (33.3)	
15-35 V	12 (35.3)	22 (64.7)	
>35	2 (22.2)	7 (77.8)	

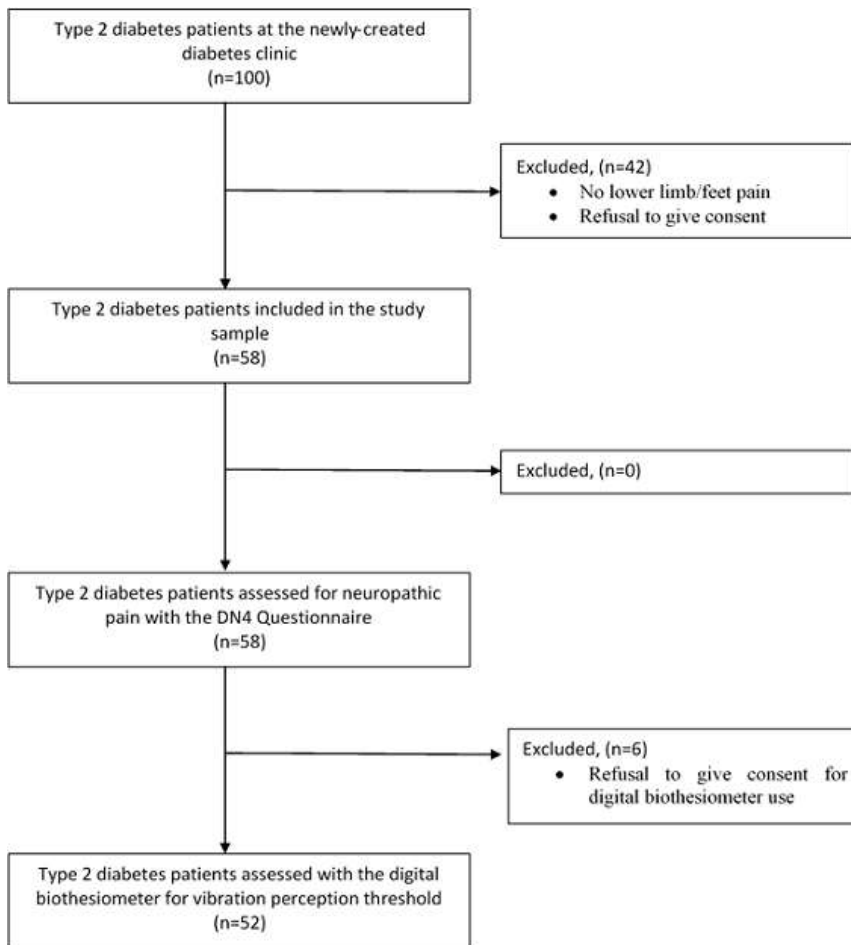
SBP, Systolic blood pressure. DBP, Diastolic blood pressure. BMI, Body mass index. VPT, Vibration Perception Threshold. IQR, Interquartile range. SD, Standard deviation

**Table 3:** diagnostic accuracy of DN4 questionnaire score compared to VPT

Parameters	DN4 Score
Sensitivity (%)	67.4%
Specificity (%)	66.7%
PPV (%)	90.6%
NPV (%)	70.0%

DN4, douleur neuropathique 4. VPT, vibration perception threshold. PPV, positive predictive value. NPV, negative predictive value





**Figure 1:** flow diagram of participant recruitment in the study