

# The prevalence and associated factors of neuropathic pain symptoms in a cohort of multi-ethnic Malaysian patients with diabetes mellitus

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## Abstract

**Objective:** To determine prevalence and factors associated with neuropathic pain symptoms in a multi-ethnic cohort of Malaysian adult diabetic patients. **Methods:** This was a prospective cross-sectional observational study of hospital-based diabetic outpatients in Malaysia. Subjects were interviewed for their demographic data and medical history. The painDETECT questionnaire was used to screen for neuropathic pain symptoms and pain intensity was assessed using the numeric pain rating scale (NPRS). Neuropathy symptoms and signs were assessed using the Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS). **Results:** Of 242 patients, 140 (58%) were women, with a mean age of  $61 \pm 11.4$  years (range 21 to 81). Ninety nine (40.9%) were Malay, 64 (26.4%) Chinese, 76 (31.4%) Indian and three (1.2%) were Eurasian. Mean duration of diabetes was  $15.9 \pm 9.8$  years (range 1 to 53) and 232 (95.9%) patients had Type II diabetes. Peripheral neuropathy, based on NSS and NDS criteria, was found in 83 (34.3%). Thirteen (5.4%) patients were found to likely have neuropathic pain symptoms and this was independently associated with peripheral neuropathy (OR = 3.40, 95% confidence interval (CI): 1.04, 11.14) and Indian ethnicity (OR = 5.44, 95% CI: 1.50, 19.57). Patients with neuropathic pain had higher average pain intensity scores.

**Conclusions:** The prevalence of neuropathic pain symptoms in a Malaysian DM patient cohort was low and was associated with the severity of neuropathy symptoms and Indian ethnicity. The causes for ethnic differences are unknown and could be due to socio-cultural or physiological differences in neuropathic pain perception.

**Keywords:** Diabetes mellitus, neuropathic pain, prevalence, ethnic differences

## INTRODUCTION

Diabetes mellitus (DM) is a growing worldwide epidemic.<sup>1</sup> In Malaysia, with increasing urbanisation, rapid economic development and changing lifestyle, the prevalence of DM has almost quadrupled from 6.3% in 1986 to 22.6% in 2013.<sup>2</sup> Peripheral neuropathy is a common long-term complication of DM, with an estimated prevalence of between 10 to 30% of patients depending on whether studies were community or hospital-based.<sup>3</sup> A hospital-based cross-sectional study in the United Kingdom, found an overall prevalence of 28.5% for diabetic peripheral neuropathy and this was associated with age, duration of diabetes and was more common in type II diabetes.<sup>4</sup>

A common and significant symptom of diabetic peripheral neuropathy is pain, which causes significant morbidity and loss of function.<sup>1,3,5,6</sup> A study from northwest England found that about a third of DM outpatients had painful symptoms and about one-fifth were determined to have painful diabetic neuropathy.<sup>7</sup> Painful neuropathic symptoms were more common in women, type II diabetics and in those of South Asian ethnicity.<sup>7</sup> Other studies from UK, France, Middle East and South Africa have estimated that about 20 to 54% of patients had diabetic peripheral neuropathic pain<sup>8-13</sup>, while in Asia, a study from Korea reported a prevalence of 14.4% for painful diabetic neuropathy in Type 2 DM patients.<sup>14</sup>

In Malaysia, peripheral neuropathy has previously been found in about 50% of diabetic

patients, but there are as yet no estimates on the prevalence of painful diabetic neuropathy (15,16). Therefore, the objective of this study was to determine the prevalence of neuropathic pain symptoms in a multi-ethnic group of Malaysian DM patients and to assess its associated factors. The presence of neuropathic pain symptoms was determined by using a validated screening tool, the painDETECT questionnaire (PD-Q).<sup>17</sup>

## METHODS

This was a prospective, cross-sectional, observational study performed on an unselected group of adult diabetic outpatients seen at the University of Malaya Medical Centre (UMMC), an academic tertiary hospital in Kuala Lumpur, Malaysia. Patients were included if they had a confirmed diagnosis of diabetes mellitus and gave written informed consent to participate. The study was approved by the UMMC Medical Ethics Committee (MEC ID No: 956.61).

Subjects previously confirmed to have diabetes mellitus and on regular follow-up at the hospital specialist diabetes clinic, were interviewed by medical students who were especially trained for this study by one of the senior authors, a consultant neurologist. The interview was conducted using a standard pre-designed questionnaire and information was obtained on their demographic characteristics (i.e. age, gender and race), type and duration of their diabetes, smoking and alcohol consumption, other medical history and medication. Their most recent glycosylated haemoglobin (HbA1c), serum urea and creatinine levels were recorded.

The presence and severity of neuropathy symptoms and signs were assessed using the modified Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) (Table 1).<sup>4,7</sup> Neuropathy symptoms were classified into mild (NSS 3-4), moderate (NSS 5-6) and severe (NSS 7-9) while neuropathy signs were also classified mild (NDS 3-5), moderate (NDS 6-8) and severe (NDS 9-10).<sup>4</sup> The presence of moderate signs (NDS  $\geq 6$ ) regardless of symptoms or mild signs (NDS  $\geq 3$ ) with moderate symptoms (NSS  $\geq 5$ ) was used as criteria for peripheral neuropathy, a previously used definition in a study on the prevalence of diabetic peripheral neuropathy in hospital-based UK population.<sup>4</sup>

Subjects were asked if they experienced any form of chronic pain (defined as a duration of at least three months) and to rate the average intensity of pain during that period, using the

Numeric Pain Rating Scale (NPRS), which ranged from 0 (=no pain) to 10 (=worst possible pain). The painDETECT questionnaire (PD-Q) was used to screen for the presence of neuropathic pain symptoms. This consisted of nine items of which seven were on sensory symptoms and scored between 0 (=never) and 5 (=very strongly) and two items on the course of the pain and its radiation respectively (15). The total score ranged from -1 to 38, with a score of  $\geq 19$  indicating that a neuropathic pain component is likely; 13-18, unclear (but neuropathic pain component could be present);  $\leq 12$ , indicating that a neuropathic pain component is unlikely.<sup>17</sup> The English version of PD-Q was used as it is a widely spoken language in Malaysia.

Comparisons were made between neuropathic pain and non-neuropathic pain (unclear and unlikely neuropathic pain) groups to look for possible associated demographic or clinical factors of neuropathic pain. Bivariate analyses were carried out using the Chi-Square test for categorical variables (using the Fisher exact test if the number in the cell was  $< 5$ ) while Student's *t* or Mann-Whitney *U* tests were used for continuous variables which were normally or non-normally distributed respectively. Correlations between two different variables were assessed by the Spearman correlation coefficient. The criterion for statistical significance was  $p \leq 0.05$ . To determine independently predictive factors for neuropathic pain, forward stepwise multivariate logistic regression analysis was carried out. Significant variables on bivariate analyses as well as other potentially significant and clinically relevant factors were entered into the model and odds ratios (OR) calculated at the 95% confidence interval (CI). Data were analysed using SPSS version 20.

## RESULTS

Table 2 details the demographic and clinical characteristics of the study patients. Of the 242 subjects recruited, 140 (57.9%) were women and 102 (42.1%) were men. Ninety-nine (40.9%) were Malays, 76 (31.4%) were Indians, 64 (26.4%) were Chinese and three (1.2%) were Eurasian (mixed Caucasian and Asian). Their ages ranged from 21 to 81 years (mean  $61 \pm 11.4$ ). Age of onset of DM was 14 to 70 years (mean  $45.0 \pm 11.3$ ) and duration of DM since diagnosis was one to 53 years (mean  $15.8 \pm 9.8$ ). The majority, 232 (95.9%), had Type 2 DM and only 10 (4.1%), had Type 1 DM. Their HbA1c values ranged from 4.8 - 17.1% (mean  $8.2 \pm 2.0$ ) and serum

**Table 1: Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS)<sup>4</sup>**

<b>Symptoms</b>		
Burning, numbness, tingling	2	
Fatigue, cramping, aching	1	
None	0	
<b>Location</b>		
Feet	2	
Calves	1	
Elsewhere	0	
<b>Timing of symptoms</b>		
Nocturnal exacerbation	2	
Present during day and night	1	
Present during the day only	0	
Symptoms wake patient up from sleep	1	
<b>Manoeuvres to reduce symptoms</b>		
Walking	2	
Standing	1	
Sitting/Lying	0	
<b>Signs</b>	<b>Right</b>	<b>Left</b>
<b>Ankle reflex</b>		
Absent	2	2
Present only with re-inforcement	1	1
Present	0	0
<b>Pin-prick</b>		
Absent/reduced	1	1
Present	0	0
<b>Vibration</b>		
Absent/reduced	1	1
Present	0	0
<b>Temperature (cold tuning fork)</b>		
Absent/reduced	1	1
Present	0	0

Symptoms: Mild (NSS 3-4), Moderate (NSS 5-6), Severe (NSS 7-9)

Signs: Mild (NDS 3-5), Moderate (NDS 6-8), Severe (9-10)

creatinine levels ranged from 33 - 877  $\mu\text{mol/L}$  (mean  $125.3 \pm 124.0$ ). One hundred and sixty (66.1%) had associated hypertension and 77 (31.8%), hyperlipidaemia. Thirty nine (16.1%) were current or previous smokers and 33 (13.6%) were current alcohol consumers. Of 165 subjects (68.2%) who complained of chronic pain (duration of at least three months), median NPRS score was 5.0 (range from 2-10).

One hundred patients (41.3%) had mild, 74 (30.6%) moderate and 53 (21.9%) severe neuropathy symptoms while 75 (31.4%) had

mild, 44 (18.2) moderate and one (0.4%) severe neuropathy signs respectively. There was no correlation between NSS and NDS scores (Spearman  $\rho = 0.121$ ,  $P=0.059$ ) but NSS and NDS correlated with average pain intensity (NPRS) scores (for NSS, Spearman  $\rho = 0.575$ ,  $P<0.0001$ ; for NDS, Spearman  $\rho = 0.169$ ,  $P=0.042$ ). Eighty three (34.3%) patients fulfilled the NSS/NDS criteria for peripheral neuropathy. There were no significant ethnic differences in terms of NSS and NDS scores or in those defined to have peripheral neuropathy.

**Table 2: Demographic and clinical variables of patients with diabetes mellitus with and without neuropathic pain symptoms (based on PD-Q) in the study**

Factors	Overall	Likely neuropathic pain	Unclear or unlikely neuropathic pain	P-Value*
<b>Number of subjects (%)</b>	242 (100)	13 (5.4)	229 (94.6)	
<b>Age (mean <math>\pm</math> SD)</b>	61.0 $\pm$ 11.4	56.2 $\pm$ 12.2	61.2 $\pm$ 11.3	0.107
<b>Gender: Female/Male (%)</b>	140/102 (57.9/42.1)	8/5 (61.5/38.5)	132/97 (57.6/42.4)	0.782
<b>Ethnicity</b>				
<b>Malay, n (%)</b>	99 (40.9)	5 (38.5)	94 (41.0)	
<b>Chinese, n (%)</b>	64 (26.4)	0 (0)	64 (27.9)	
<b>Indian, n (%)</b>	76 (31.4)	8 (61.5)	68 (29.7)	
<b>Eurasian, n (%)</b>	3 (1.2)	0 (0)	3 (1.3)	0.036
<b>Type 2 Diabetes Mellitus(%)</b>	232 (95.9)	13 (100)	219 (95.6)	1.000
<b>Duration of Diabetes (mean <math>\pm</math> SD)</b>	15.8 $\pm$ 9.8	14.8 $\pm$ 8.6	15.8 $\pm$ 9.8	0.816
<b>Hypertension (%)</b>	160 (66.1)	6 (46.2)	154 (67.2)	0.118
<b>Hyperlipidemia (%)</b>	77 (31.8)	1 (7.7)	76 (33.2)	0.067
<b>Smoker (current and previous) (%)</b>	39 (16.1)	1 (7.7)	38 (16.7)	0.699
<b>Alcohol consumption (current) (%)</b>	33 (13.6)	1 (7.7)	32 (14.0)	1.000
<b>Average Pain intensity (NPRS) (median, range)</b>	5 (0.5-10)	8 (7-10)	5 (0.5-10)	<0.002
<b>Neuropathy Symptom Score (NSS):</b>				
<b>Normal (NSS 0-2)</b>	15 (6.2)	0 (0)	15 (6.6)	
<b>Mild (NSS 3-4)</b>	100 (41.3)	1 (7.7)	99 (43.2)	
<b>Moderate (NSS 5-6)</b>	74 (30.6)	7 (53.8)	67 (29.3)	
<b>Severe (NSS 7-9)</b>	53 (21.9)	5 (38.5)	48 (21)	0.022
<b>Neuropathy Disability Score (NDS):</b>				
<b>Normal (NDS 0-2) (%)</b>	122 (50.4)	4 (30.8)	118 (51.5)	
<b>Mild (NDS 3-5) (%)</b>	75 (31)	5 (38.5)	70 (30.6)	
<b>Moderate (NDS 6-8) (%)</b>	44 (18.2)	3 (23.1)	41 (17.9)	
<b>Severe (NDS 9-10) (%)</b>	1 (0.4)	1 (7.7)	0 (0)	0.044
<b>Peripheral neuropathy (NSS<math>\geq</math> 5 and NDS &gt; 3; or NDS &gt; 6) (%)</b>	83 (34.3)	8 (61.5)	75 (32.8)	0.033
<b>HBA1c (%) (mean <math>\pm</math> SD)</b>	8.2 $\pm$ 2.0	8.3 $\pm$ 2.3	8.2 $\pm$ 2.0	0.991
<b>Creatinine (<math>\mu</math>mol/L) (mean <math>\pm</math> SD)</b>	125.3 $\pm$ 124.0	193.0 $\pm$ 200.2	121.4 $\pm$ 117.4	0.070

\*Chi-square test (Fisher exact test if no. in a cell < 5) for categorical variables; student's t test and Mann-Whitney U for continuous variables; statistically significant if  $P \leq 0.05$

PD-Q: painDETECT questionnaire

Using the PD-Q, 13 (5.4%) patients were classified as likely having neuropathic pain symptoms while 29 (12%) were unclear and 200 (82.6%) were unlikely to have neuropathic pain. Of those with neuropathic pain symptoms, 8 (61.5%) fulfilled the NSS/NDS criteria for

peripheral neuropathy. If only patients with chronic pain were considered, the frequency of neuropathic pain symptoms was 7.9% (13 of 165 subjects). Associations with neuropathic pain symptoms are summarised in Table 2. There were significant associations with NSS ( $P=0.022$ ) and

NDS scores ( $P=0.044$ ), peripheral neuropathy based on NSS/NDS criteria ( $P=0.033$ ) and higher average NPRS scores ( $P<0.0002$ ). There were also ethnic differences for neuropathic pain symptoms (Table 2). The prevalence rate of neuropathic pain symptoms among Malays, Indians and Chinese were 5.1% (5 of 99), 10.5% (8 of 76) and 0% (0 of 64) respectively. Comparing between ethnic groups, Indians were more likely than non-Indians (10.5% versus 3%,  $P=0.027$ ) to have neuropathic pain symptoms. Serum creatinine levels were higher in subjects with neuropathic pain symptoms but this was not statistically significant (193 versus 121.4  $\mu\text{mol/L}$ ,  $P=0.07$ ). Neuropathic pain symptoms were not significantly associated with gender, age, duration of DM, hypertension, hyperlipidaemia, smoking, alcohol consumption or HBA1c levels. Multivariate logistic regression analyses found that factors independently associated with neuropathic pain symptoms were peripheral neuropathy (based on NSS/NDS score) (odds ratio (OR) = 3.40, 95% confidence interval (CI): 1.04, 11.14), Indian ethnicity (OR =5.44, 95% CI: 1.50, 19.57) and serum creatinine levels (OR = 1.004, 95% CI: 1.001, 1.007). ).

## DISCUSSION

The prevalence of subjects likely to have neuropathic pain symptoms in our cohort of patients was 5.4%. This was much lower than the previously reported prevalence neuropathic pain of 13% to 34% in other populations.<sup>7-14</sup> However, these studies are not strictly comparable as there are differences in sample size, study population (hospital or population-based) and the definition used for neuropathic pain. Some studies used screening tools based on verbal pain descriptors to identify neuropathic pain symptoms.<sup>18</sup> These include the Douleur neuropathique en 4 questions (DN-4), Leeds assessment of neuropathic symptoms and signs (LANSS), neuropathic pain questionnaire (NPQ), ID Pain and the PD-Q, which was used in this study. Using the DN4 or S-LANSS, studies in different populations have found the prevalence of neuropathic pain symptoms in DM patients to range from 16 to 54%.<sup>8-13</sup> Others studies utilised clinical neuropathy symptoms and physical examination scores (e.g. NSS and NDS) and hence could likely be more precise in their definition. However, using NSS scores to identify neuropathic pain symptoms may not be as specific. For example, the Northwest England study defined neuropathic pain symptoms by an NSS Score  $\geq 5$  and reported a prevalence

of neuropathic pain symptoms of 34%, but the NSS does not discriminate between painful and non-painful symptoms (e.g. symptoms of burning, tingling or numbness are scored equally) and could possibly overestimate the number of subjects with neuropathic pain symptoms. An Asian study from Korea, with a more precise definition of diabetic painful neuropathy based on both VAS score and clinical symptoms and signs reported a lower prevalence at 14.4% of Type II DM patients.<sup>14</sup>

On multivariate analysis, factors independently associated with likely neuropathic pain in our DM patients are peripheral neuropathy (based on NSS/NDS criteria), Indian ethnicity and serum creatinine levels. In the five patients with neuropathic pain symptoms but not fulfilling criteria for neuropathy, the basis of their neuropathic pain is still likely peripheral neuropathy as the NSS and NDS are epidemiological screening tools and would not conclusively exclude peripheral neuropathy. Some may have asymmetrical signs or have symptoms without significant physical signs and would therefore not be classified as peripheral neuropathy. Previous studies have also found neuropathic pain in some patients not classified as peripheral neuropathy possibly for similar reasons.<sup>7,9,10</sup> Average pain intensity scores also correlated with NSS and NDS scores and are higher in those with neuropathic pain. This could suggest that neuropathic pain is related to the severity of peripheral neuropathy. However, the relationship with serum creatinine levels and neuropathic pain is unclear as the odds ratio is low (1.004) and our subject numbers small, although a previous study had reported an association with diabetic nephropathy.<sup>10</sup> We did not find any associations with previously reported factors such as age, female gender, glycaemic control (as measured by HBA1C levels), duration of DM, hypertension, hyperlipidaemia, alcohol consumption and smoking.<sup>7,10-14</sup> Other associated variables reported in other studies but not evaluated in this study, included obesity and previous cerebrovascular accidents.<sup>12-14</sup> In addition, DM patients with neuropathic pain had been reported to have significantly worse sleep, anxiety, mood and quality of life measures.<sup>10,14</sup>

In this study we compared diabetics from the different ethnic groups in Malaysia, all of whom have been resident in the country for many generations and exposed to similar environmental influences. We found that ethnic Indians are more likely while ethnic Chinese less likely to have neuropathic pain symptoms. Differences in pain perception between these

ethnic groups have been reported previously in Singapore (a country with a similar multi-ethnic composition) for other chronic pain conditions i.e. osteoarthritis and headache.<sup>22,23</sup> Our findings were also similar to the northwest England study, where South Asians (viz. ethnic Indians) were found to have a higher prevalence of painful neuropathic symptoms compared to Europeans or African Caribbean DM patients, although they had lower prevalence of clinical peripheral neuropathy.<sup>7</sup> Differences between ethnicities could be explained by differences in socio-economic factors, cultural background, psychological sensitivities (e.g. expectations, pain beliefs) or even biological responses to pain.<sup>24</sup> However, in another study in which black South Africans were reported to have higher risk for neuropathic pain compared to other ethnic groups, the authors postulated that this could be due to a relatively higher prevalence of human immunodeficiency virus (HIV) seropositivity among that ethnic population and therefore higher prevalence of associated painful HIV neuropathy.<sup>11</sup>

The main limitations of this study are its relatively small sample size, the use of convenience sampling and that subjects were drawn from single tertiary hospital clinic. These factors contribute the bias in the study. However, as the study objective was neuropathic pain, bias would have been to more patients with pain. In fact, the majority of responders had chronic pain (68.2%) although prevalence of neuropathic pain was low.

Another limitation was the use of a screening tool, the PD-Q, to identify neuropathic pain symptoms. The diagnosis of neuropathic pain has been revised to provide emphasis on evidence of pain as a direct consequence of a lesion or disease of the nervous system, with a grading system which requires data from clinical history, physical examination and investigations to define possible, probable and definite neuropathic pain respectively.<sup>25,26</sup> Nevertheless, screening tools, although not diagnostic, can provide useful epidemiological data on neuropathic pain symptoms in the population studied. We used the PD-Q as it has been shown to be a reliable screening instrument of neuropathic pain across different conditions including painful diabetic neuropathy.<sup>17-21</sup> In a study to compare the original 9-item PD-Q with the 7-item version (which excluded the spatial and temporal components of pain), the positive predictive value of PD-Q for diabetic neuropathic pain was 85%.<sup>21</sup> However, the PD-Q, as with other neuropathic pain screening

tools may miss up to 10 to 20% of subjects with clinically diagnosed neuropathic pain.<sup>18</sup> Furthermore, the PD-Q has an “unclear” group in which a neuropathic pain component could still have been present. Therefore, the reported frequency of neuropathic pain in this study is likely to be an underestimate of the actual prevalence in the population.

In conclusion, the prevalence of neuropathic pain symptoms in a cohort of Malaysian diabetic outpatients is found to be low and is associated with severity of neuropathy symptoms, higher average pain intensity scores and Indian ethnicity. Recognition of ethnic differences could suggest a role of socio-economic, cultural and even genetic factors in the perception of neuropathic pain.

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## DISCLOSURE

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