Clinical evaluation of painful diabetes peripheral neuropathy in type 2 diabetes patients: lessons from expatriates in the United Arab Emirates.

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Prescriptive Framework for Clinical Assessment of pDNP among T2DM Patients in the United Arab Emirates

Abstract

Background

High prevalence of Type 2 Diabetes Mellitus (T2DM) in the United Arab Emirates (UAE) makes it imperative to screen and manage of DPN at priority. Considering high number of expats from different ethnicity a more thorough approach is necessary. Unfortunately, there are very few studies addressing this issue.

Methods

The study uses chi-square test to investigate the dependence of progression of DPN on the ethnic origin. The study uses Pearson Correlation to find association between three prevalent scales used for the measurement of painful diabetes peripheral neuropathy (pDNP). Student t-test was used futher to investigate the significance of the association. The participants of the study are resident of the UAE and the sampling method used for the study is non probabilistic purposive sampling.

Results

With p-value (0.004) and p-value (0.015) the study concludes that DPN risk is dependent on ethnic origin of the residents. The study further found that there is significant association between three scales for measuring pDPN , DN4, NSS, and LANNS. The p-value for all pairwise comparison for strength of association between scales was found significant at level of significance 0.05.

Conclusion

The study concludes that risk of DNP is high in Arab origin residents in UAE and the reasons behind the find need to empirically tested to customize its management. The study further finds significant association between the score of the three scales used for measuring pDNP. We recommend the use of DN4 scale as first instrument for mass screening.

Keywords: T2DM, Neuropathy, pDNP, Screening, Framework, UAE

1. Introduction

Diabetes peripheral neuropathy (DPN) is one the most debilitating and long-term standing complications of type 2 diabetes mellitus [1.2]. It leads to multiple numbers of vascular, musculoskeletal, autonomic, and neurological complications. The screening and management of DPN and its complication are an extreme social burden because of its intensive long-term standing nature [3]. Studies have reported that 50 % of people with long-term diabetes have DPN and 50 % of them suffer from painful symptoms so called "Painful Diabetic Neuropathy" [4]. Studies have also suggested that 60-70% of diabetic foot ulcers are primarily neuropathic in origin [3]. Thus painful diabetic peripheral neuropathy could be an important clinical manifestation of type 2 diabetes mellitus and should be assessed well in clinical settings.

1.1.Painful Diabetic Peripheral Neuropathy

Painful diabetic peripheral neuropathy (pDPN) is a serious concern that demands proper attention and management. It is defined as pain arising from direct consequences of abnormalities within the somatosensory system among individuals with diabetes mellitus [4]. It can be diagnosed with classical signs and symptoms of neuro-ischemic pain. Associated pain has been clinically described as tingling, numbness, sensitivity to touch, burning, electrical, stabbing, shock-like feeling, paresthesia, hypoesthesia, and allodynia [5]. It could be associated with diurnal variation and thus found to be increased typically at night which disturbs sleep. Pain may start at both feet initially and progress to involve calves, hands, and fingers [6]. Studies have also reported that the pain in DPN is often excruciating but may revert spontaneously [7]. The impact of pDPN on an individual's quality of life could be significant (1). It can affect the entire personality of an individual. Several studies have highlighted the impact of neuropathic pain on the quality of life in type 2 diabetes mellitus patients. A study reported that all areas of life including mood, sleep, independence, self-worth, work skills, and the interpersonal relationship could be easily disturbed [5]. Similarly, another study concluded that the presence of pDPN is closely associated with greater co-morbidities in terms of limb infection [6]. Tenfold greater limb amputation and higher healthcare service costs were reported in patients with painful neuropathy compared to non-painful DPN [6]. Some authors have also suggested that health-related QoL in painful peripheral

neuropathy gets significantly affected [3,8,9]. The study done by Boulton et al. 1998 reported significantly lower scores in five out of the six domains (health-related quality of life) that consisted of energy, sleep, pain, physical mobility, and emotional stress [10]. Studies have also shown a significant relationship between pain intensity and the worsening of self-assessed health status [11].

1.2.Prevalence of pDPN

The prevalence of pDPN has been reported by a few authors. However, the majority of these studies have been conducted and reported in a small geographical area. A study from six geographical areas of France reported the prevalence of DPN and pDPN (1). The study reported a prevalence rate of 11% & 8% for DPN & pDPN respectively. It was also suggested that 78% of the participants with DPN experienced pain, further classified as mild (17%), moderate (49%), and severe (35%). A study conducted in the United States by Schumacher and Scott 2014 reported that 37 out of 71 participants who completed the study reported signs and symptoms of pDPN (6). An overall prevalence of 26% pDPN was reported in a study in the United Kingdom by Davies et al.(9). From a hospital-based study, a point prevalence of 11 % pDPN was estimated among type 2 diabetes above 60 years of age in agreement with a similar study conducted in Germany [12]. Also, a study done on insulin-treated participants reported a prevalence of 11% pDPN and 25 % in the hospital/clinic population [13]. The study from Belgium reported that out of 478 participants, 157 were found to have neuropathic pain, and an overall prevalence rate of pDPN constituted 14.1%. The prevalence was significantly higher in Type 2 diabetes compared to Type 1 (17.9% vs 5.8%; $P = 0.002$, after adjustment for age and diabetes duration). Similarly, the prevalence rate of 14.4 % of pDPN was found in Korea [14]. On the contrary, the Middle East and North Africa (MENA) regions reported the highest prevalence rates for DPN in the entire world. For instance, the highest prevalence rate was suggested in Egypt (61.3%), Jordon (57.5%), Lebanon (53.9%), and the Gulf States (37.1%) [15] . However, based on our literature review, we found that the data on screening and assessment of pDPN is still lacking in the United Arab Emirates.

1.3.Assessment of pDPN

Assessment of pDPN includes several tools and questionnaires reported in many studies. The use and consistent development of these assessment outcomes could be closely related to the

pathogenesis of pDPN. It was suggested that painful symptoms in the diabetes mellitus population were caused by pure small fibers neuropathy. Therefore, painful neuropathy could be measured using Quantitative sensory testing (QST) that aims to test specific fibers type responses to external stimuli and record psychological responses [16]. Given these findings, the most popular index tests used for neuropathy screening are Michigan Neuropathy Screening Instrument (MNSI), Neurological Symptom Score (NSS), Neuropathy Symptom Profile (NSP), Diabetic Neuropathy Symptoms Score (DNS), Neuropathy Disability Score (NDS), Neuropathic Impairment Score in the lower limb (NIS-LL), Diabetic Neuropathy Examination (DNE), Clinical Neurological Examination (CNE), and Toronto Clinical Scoring System (TCSS). Since the role of the index test is subject to variability, alternative objective measures like electrodiagnosis and quantitative sensory and autonomic function tests may be required for confirmation. E.g. some alternative tests include the pairing of index tests with Nerve conduction studies. However, since it is difficult to use this alternative test in clinical practices, Index tests have been used more effectively in clinical settings. Likewise, the most commonly used valid and reliable tools for detecting neuropathic pain in DPN are The Leeds Assessment of Neuropathic Symptoms and Signs (LANNS) pain scale, Douleur Neuropathique 4 Questions (DN4), Neuropathic Pain Symptom Inventory, Brief Pain Inventory Modified (Short-Form)[17].

The assessment and management of pDPN is an area of vast research. Previous studies have suggested a few important pharmacological drugs. However, to date, no treatments have proven to be extraordinarily successful and satisfying. The major reason for this could be a vague presentation of symptoms. The most common drugs for the treatment of pDPN are tricyclic antidepressants (TCAs) and anti-epileptics. In a randomized controlled trial, Carbamazepine was first used for pDPN in 1969 whereas Amitriptyline was first used in 1977. However; the first drug approved for treatment of pDPN was Duloxetine in 2004(5). Following which Pregabalin has been commonly used after receiving the approval from Food and Drug Administration, United States. In a study, conducted by Huizinga and Peltier 2007 it was suggested that it may be difficult to achieve complete relief from any of the pharmacological agents and other combinations of treatment should be tried with a higher degree of success [5]. Studies have shown a positive effect of low-level laser therapy on diabetic foot ulcers and neuropathic pain [2]. For effective management of the condition, it would be first necessary to identify and assess the pDPN.

Therefore, the study aimed to clinically screen and assess the pDPN among type 2 diabetes mellitus in the United Arab Emirates.

The study primarily investigates following two research questions:

1. Is DPN risk dependent on the ethnic origin of the residents in the UAE?
2. What is the rationale for multiple scale for pDPN in diabetes management ?

The next section of the study discusses material and methods in detail followed by result and discussion about inferences drawn from them. Finally study concludes with implications , limitations and future directions of research.

2. Material and Methods

This section discusses the study design the scale used in assessment and hypothesis proposed and method used for its testing.

2.1.*Study Design and Settings*

The cross-sectional study was conducted at Thumbay University Hospital, Gulf Medical University Ajman UAE.

A total of 283 male hyperglycemic patients with diagnosed Type 2 Diabetes Mellitus participated in the study under the purposive sampling method. A detailed clinical assessment for DPN was performed following which a total of 178 participants were found to have positive signs and symptoms. Out of 178 DPN participants, 76 participants had complaints of pain in the foot and thus further screened and assessed for pDPN.

Study Procedure: Approval from the Institutional Ethics Committee was obtained. This was followed by a signed informed consent from all the participants. The detailed procedure of data collection was explained to all participants by one of the examiners. An overview of the use of the diabetes peripheral neuropathy assessment and specific questionnaires was also given to each participant before data collection. The process of data collection has been described under the following segments.

Diabetes History: A detailed relevant history was obtained from all the participants. It consisted of demographic and anthropometry characteristics, occupation of the participant, complete address and their living environment, socio-economic history, latest biochemistry (fasting blood sugar levels, Post- Prandial blood sugar levels & HbA1c), duration of diabetes, type of diet, type of medical treatment (oral hypoglycemic/ Insulin, ayurvedic, etc.), family history of diabetes, and lipid profile,

Pain History: This was carefully noted and the majority of the participants reported complaints like burning, tingling, numbness, altered sensation, inability to sense feet while walking, slipping of footwear, unsteadiness while walking, weakness, fatigue, and pain. Symptoms typically increased at night.

Screening for DPN: A detailed assessment was done to determine the presence of diabetes peripheral neuropathy. These included specific vascular, musculoskeletal, autonomic, and neurological examinations as described below.

Vascular Assessment: These consisted of pedal pulse palpation, Ankle-brachial Index (ABI), skin temperature (palpation), capillary refilling of toenails, and vascular claudication.

Sensory Assessment: It consisted of protective sensation testing using 10 g Monofilament for intact touch, pinprick hot and cold, and vibration sense (Biothesiometer). Ankle and knee reflex testing were also conducted.

Motor Assessment: The important parameters for testing under the motor assessment and examination were muscle strength testing (Medical Research Council Grading) for intrinsic foot muscles and proximal muscles of the lower extremity (extensor hallicus longus, tibialis anterior, gastro-soleus, quadriceps, hamstring, and hip gluteus Medius, minimus & maximus), muscle length testing (gastro-soleus, quadriceps, hamstring, and Iliotibial band. Toe deformities like bunions, clawing, hammer, and Charcot's foot were also assessed under motor examination. Callus, fissures, and foot arch was important part of the clinical assessment.

Autonomic System: These included testing of blood pressure, dryness of skin, discoloration of the skin, and nail pathology.

2.2.Scales Used in the Study

The clinical confirmation of DPN was made with findings from the MNSI scale score. Important components assessed were altered ankle reflex response, sensory testing using 10 g Monofilament and a Vibration Pressure Threshold [2].

MNSI: Michigan Neuropathy Screening Instrument is a widely used valid and reliable tool for DPN screening in the clinical setting [18]. Although MNSI does not specifically target to score pDPN it has a targeted question number 2 for burning pain under the patient version. MNSI has two parts where the first part (questionnaire) has a cut-off score of 7 and the second part (foot examination) has a cut-off score of 2.5 for confirmation of DPN [19]. The first part was given to all participants in English as well as locally translated Arabic language.

Participants with confirmed DPN on MNSI (n=178) were further screened and assessed for pDPN based on findings from the respective scales. The following scales were used to determine the painful diabetic peripheral neuropathy (pDPN) in this study as they have a higher specificity and sensitivity to detecting pain of neuropathy origin [19].

DN4: Douleur Neuropathique 4 Questions- It is one of the most popular questionnaires for the diagnosis of neuropathic pain with high specificity. The maximum score is 10 and a score of >4 was considered as pDPN.

NSS: Neuropathy Symptoms Score – The scale comprises specific questions for pain experience and discomfort in the legs. The maximum score for each foot is 9 and a score of 0-3 was considered as the pain of vascular origin and 3-9 as neuropathy origin.

LANNS: The Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale –It has two components A (pain questionnaire) & B (Sensory Testing). This scale could most suitably be confirming the presence of pDPN. A score of ≥ 12 has a neuropathic mechanism likely to be contributing to the patient's pain.

2.3. Proposed Hypotheses and Statistical Methods

Based on the above research questions following hypothesis are need to be tested:

H1A: DPN Risk using MNSI independent (Part-A)of ethnic origin of expats in the UAE
H1B: DPN Risk using MNSI independent (Part -B) of ethnic origin of expats in the UAE
H2A: There is not any significant association between pDNP Score of DN4 and NSS
H2B: There is not any significant association between pDPN Score of NSS and LANNS
H2C: There is not any significant association between pDPN Score of LANSS and DN4

For testing the first set of hypothesis Chi-Square test of independence was used. While for remaining hypotheses Pearson Correlation was used calculate the association between score on various scale. Further to test the significance correlation t-test was performed.

3. Results

The anthropometric characteristics of all participants have been shown in Table 1. Out of 283 participants, a total of 178 participants were found to have a score corresponding to diabetic peripheral neuropathy on the MNSI scale. The findings of DPN cases are represented in Table 2A, 2B. Out of 178 DPN participants, 42 were found to have painful symptoms and the scores correlating for painful neuropathy on each scale which have been presented in Table 3.

Table 1. Demographic characteristics of all participants (N= 283, all males)

Age	**Mean**	**S. D**
Height in cm	169	6.57
Weight in kg	83	9
BMI	32.42	3.69
FBS	188	42
PPBS	256	67
HbA1c	7.1	1.3
Participants from Indian Subcontinent Origin	**N= 186**	
Participants from Arabic Origin	**N= 97**	

Table 2 A: DPN Risk using MNSI independent (Part-A)

MNSI- Part A Components	Indian Subcontinent Expats	Arabic Origin
	Yes	Yes
1. Are your legs and/or feet numb?	N=54	N= 33
2. Do you ever have any burning pain in your legs and/or feet?	N=22	N= 19
3. Are your feet too sensitive to touch?	N= 17	N=30
4. Do you get muscle cramps in your legs and/or feet?	N= 18	N=21
5. Do you ever have any prickling feelings in your legs or feet?	N= 28	N=17
6. Does it hurt when the bed covers touch your skin?	N= 9	N=12
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	N= 20	N= 14
8. Have you ever had an open sore on your foot?	N= 13	N= 10

9. Has your doctor ever told you that you have diabetic neuropathy?	N= 38	N= 24
10. Do you feel weak all over most of the time?	N= 86	N= 48
11. Are your symptoms worse at night?	N= 64	N=34
12. Do your legs hurt when you walk?	N= 67	N=36
13. Are you able to sense your feet when you walk?	N= 69	N= 47
14. Is the skin on your feet so dry that it cracks open?	N= 104	N= 39
15. Have you ever had an amputation?	N=4	N=3

Table 2B: DPN Risk using MNSI Independent (Part-B)

Serial Number	**Indian Subcontinent Expats**			**Arabic Origin**		
1. Appearance of Feet (Altered)	N= 75			N= 32		
2. Ulceration (Present)	N= 7			N=5		
3. Ankle Reflex	Present N= 51	Reinforced N= 20	Absent N=33	Present N= 26	Reinforced N= 16	Absent N=32

4. Vibration Perception at Great Toes	Present N= 37	Decreased N= 47	Absent N=20	Present N= 27	Decreased N= 31	Absent N=16

Table 3. Findings for painful diabetic peripheral neuropathy (N=42)

pDPN Scales	Mean	S. D
DN4	5.6	2.8
NSS	4.5	1.3
LANNS	15.7	2.6

$\chi 2$ Statistics was calculated using Observed Frequency (O) and Expected Frequency (E) with help of equation (Eq-1). The most severe situation amputation is removed from the contingency as frequency for both category has less than five.

$$\chi 2 = \frac{(O-E)^2}{E} \qquad (1)$$

To determine if a correlation coefficient is statistically significant t-score (t) was calculated using equation (Eq-2). Where r is Pearson correlation coefficient.

$$t = \frac{r\sqrt{n-2}}{1-r^2} \qquad (2)$$

The statistical software used for the study is R. The level of significance used for evaluating all five hypothesis is 0.05. The result is summarized in Table-4.

Table 4: Summary of the Results of Hypothesis Testing

Hypothesis	Test score and p-Value (2-tailed)			Inferences Drawn
H1A	$\chi 2$ (30.43)		p-value (0.004)	Null Hypothesis is rejected
H1B	$\chi 2$ (4.29)		p-value (0.231)	Null Hypothesis is rejected
H2A	r (0.49)	t (6.85)	p-value (4.5E-11)	Null Hypothesis is rejected

H2B	r (0.47)	t (10.15)	p-value (7.86E-21)	Null Hypothesis is rejected
H2C	r (0.52)	t (11.99)	p-value (4.82E-27)	Null Hypothesis is rejected

4. Discussion

The present study has included type 2 diabetes mellitus participants from Indian subcontinent expats and Arabic origin. Out of a total of 283 participants, the participants from the expats were higher equivalent to 65 % (n= 186 out of 283), whereas the Arabic origin contributed to the rest 35%. The findings from the MNSI score suggested that a total of 178 out of 283 participants were screened with DPN which accounts for 62% of the studied population in consensus with previous findings in MENA region (15). The results highlights higher rate of DPN in the United Arab Emirates compared to other geographical areas on the globe accounting to 50% among type 2 diabetics (4). The reason for the variation could be attributed to the cultural, social and demographic differences in the UAE population majorly contributed by the Indian subcontinent expats. Table 1, represents the demographic characteristics of all participants suggesting a mean value of 256 mg/dL for post prandial blood sugar level whereas the mean value of HbA1c was 7.1 %. Higher values of HBA1c has been shown to positively correlate with diabetes peripheral polyneuropathy among diabetic population (20). It has been reported that HbA1c is an index of average glycemic control over past 3 months and could be used to predict the risk of various complications of diabetes including DPN (21),(22),(23). It could be suggested that higher cases of DPN could be attributed to higher mean values of HbA1c among the UAE population as seen in our study.

The present study highlights the ethnic differences for contribution of diabetes burden in the UAE. Though the number of participants in the study were comparatively less compared to expats (N=97), the prevalence of DPN was higher among the Arab origin. Out of total 178 cases of DPN from 283 participants, the Indian subcontinental expats and Arab origin contributed for 104 cases (58%), 74 cases (42 %) for DPN respectively in the studied population. If we analyse the data in other terms, we could suggest that the Indian subcontinent expats contributed to 36% of DPN cases individually (104 out of 283), whereas the Arab origin participants contributed to 76% (N= 74 out of 97) which is significantly high. It suggests that previous studies which have reported around 60% prevalence of DPN in MENA (15) could

now be better categorized and understood with ethic and cultural differences. The findings from the MNSI screening Part A and Part B (Table 2) supported this hypothesis. We found that the there was a significant difference between the expats and Arabs for responses towards screening for DPN using MNSI. For instance, the MNSI Part A reported 52 cases for numbness (50%, n=52/104) and 22 cases (21%, n=22/104) for painful symptoms in the expats participants compared to 33 cases (34%, n=33/97) and 19 cases (19%, n=19/97) respectively in the Arabic origin participants. Similar difference was seen in Part B which reported 32 cases (30%, n=32/104) for absent ankle reflex and 20 cases (19%, n=20/104) of VPT among the Indian subcontinent expats compared to approximately 32% and 16% respective cases among the Arab origin. This could signify the differential contribution towards DPN by expats and Arab origin and further studies need to be done to understand the contribution sub factors and variables, though it is well understood that ethnic, cultural, demographic etc. differences have majorly contributed.

From the 178 screened cases of DPN, 76 participants conferred painful symptoms and thus were assessed for pDPN. The screening for pDPN was done using three different scales such as DN4, NSS, and LANNS. It was found that 42 participants in total showed positive signs for pDPN using all three scales. The findings and mean score for each scale has been presented in the Table 4. There was a positive correlation between the scales for pDPN (Table 3). There was a positive association between the DN4 and NSS (r= 0.49), NSS and LANNS (r= 0.47) and LANNS and DN4(r= 0.52). The findings suggested that all three scales could be efficiently used for assessment of pDPN among type 2 diabetes mellitus. It could also be suggested that DN4 has lesser assessment components which could be easy to use in clinical practice. However the quality of pain and details of management strategy for painful diabetic peripheral neuropathy could well be understood with the LANNS scale which is more descriptive but lengthy and consume more time.

5. Conclusions

High prevalence of diabetes in the UAE makes the study of diabetes peripheral neuropathy important as it is a common complication of diabetes. Diabetes peripheral neuropathy can significantly impact a person's quality of life. Symptoms such as pain, numbness, and tingling can affect a person's ability to perform daily activities, leading to decreased productivity and

reduced independence. Early diagnosis and treatment of diabetes peripheral neuropathy can prevent or delay the progression of the disease, thereby improving outcomes and reducing the economic burden associated with the condition.

The study concludes that risk of DNP is high in Arab origin expats in UAE and the reasons behind the find need to empirically tested to customize its management. Secondly study finds significant association between the score of the three scales used for measuring pDNP. Thus this study has one implication for theory as it suggest that risk of DNP varies among ethnic communities. While this study provides two implication for the practice. Firstly , Since there is no significant difference between three scales used , we suggest the use DN4 in large scale screening of DNP in community as it easy to administer and hence cost effective. Secondly, we can recommend use of other scales coupled with diabetic foot investigations at later stage in health centres. Thus this study provides a prescriptive approach for management of DPN and is useful for clinicians and public health professionals. One of the limitation of the study is use of non-probabilistic sampling method and a future study can address this shortcoming. There is a need of analyse the economic burden of DNP utilizing work ability and productivity loss measures.

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