ARE THE SYMPTOMS OF DIABETIC PERIPHERAL NEUROPATHY IN NIGERIAN PATIENTS OBJECTIVE? An Evaluation Using The United Kingdom Screening Test (UKST) And Bio-Thesiometry.

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ABSTRACT

Background: Symptoms suggestive of peripheral neuropathy (PN) in diabetes mellitus (DM) do not always indicate presence of underlying PN.

Objective: A pioneering study among Nigerian diabetic subjects to evaluate the objectivity of their symptoms of PN using two objective diagnostic instruments for PN the United Kingdom Screening Test (UKST) and Bio-Thesiometry.

Subjects and methods: One hundred and twenty diabetic participants and a similar number of non-diabetic controls were screened for symptoms of PN using the UKST symptoms score and subsequently separated into two groups those with symptoms of PN and those without. The "symptomatic" cases and controls were further evaluated with the UKST signs score and Bio-Thesiometry to assess the objectivity of the symptoms.

Results: Among 120 diabetic participants, 83(69.2%) had neuropathic symptoms (the symptomatic cases) while 10 (8.3%) of the 120 non-diabetic controls had neuropathic symptoms (the symptomatic controls). Among the cases, UKST signs score detected PN in 89.2% (74/83) and Bio-Thesiometry 71.1% (59/83), the difference in the ability of the two methods to detect PN in this group being statistically significant ($X^2 = 8.51$, df = 1, p < 0.01). Among the controls, UKST detected PN in 100.0% (10/10) compared to Bio-thesiometry (50.0%; 5/10), the difference in the ability of the two methods to detect PN in this group also being statistically significant ($X^2 = 4.27$, df = 1, p < 0.05, using continuity correction factor). The difference in the ability of both methods to detect PN between the cases and controls was however not statistically significant ($^2 = 0.68$, df = 1, p > 0.3)

Conclusion: The symptoms of PN among Nigerian diabetic subjects when evaluated with a gold standard for scoring the symptoms (the UKST symptoms score) are real, objective and truly indicate presence of underlying PN. Diabetic subjects presenting to medical clinics with symptoms of PN should receive serious attention and evaluation using this gold standard to detect early those with genuine PN and are at risk of foot ulceration from PN.

Key Words: Diabetic mellitus, peripheral neuropathy, United Kingdom screening test, Bio-thesiometry.

INTRODUCTION

Somatic neurological complaints of diabetes mellitus (DM) can be sensory, motor or mixed, symmetrical or asymmetrical and affect the most distal parts of the longest nerves first. Distal symmetric sensory polyneuropathy remains the most common form of neuropathy in individuals with DM [1-3] and it is much more common in the legs than in the arms of the diabetic patient [4].Peripheral neuropathy (PN) is detected by screening for typical symptoms and signs. Reduced thermal and pain sensation, numbness, and painful paraesthesias and a variety of other unpleasant sensations -tingling, burning, fatigue, aching, cramps, coldness, deadness-with profound nocturnal exacerbation, are typical of the insidious onset of sensory nerve impairment. [1,2,5] Presence of symptoms do not always indicate underling neuropathy and many diabetic legs totally lack pain sensation while at the same time experiencing a variety of painful sensations- "the painful- painless" leg. [4,6]

OBJECTIVE

To determine the objectivity of the symptoms of PN by evaluating the diagnostic performance of the United Kingdom Screening Test and Bio-Thesiometry in detecting PN among diabetic patients with symptoms of PN.

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METHODOLOGY:

Following informed consent and ethical approval, 120 diabetic patients were recruited as they presented, from the medical outpatient department (MOPD), diabetic clinic and medical wards of the Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi. This is a 250-bedded teaching hospital in Anambra State, South-Eastern Nigeria. The hospital is also complemented by 500 extra beds in outposts spread within Anambra State and manned by primary care, family and community physicians. While the hospitals primary catchment area is Anambra State with a population of about three million people, it subserves referrals from other neighbouring states in South-Eastern Nigeria. Subjects recruited included known diabetic patients (that is, subjects currently on treatment with oral hypoglycemic agents or insulin [7,8]) and newly diagnosed diabetic patients as defined by the World Health Organization (WHO) 1999 Diagnostic Criteria [9]. None of the study subjects had a current foot ulcer at the time of study.

Non-diabetic controls were also recruited from the same hospital based population as the study population. Clinical history and physical assessment was applied to exclude patients with a history of exposure to known neurotoxins and evidence of concurrent disease processes that could cause neuropathy - patients on haemodialysis for chronic renal failure, on multi drug treatment for tuberculosis, on cancer chemotherapy, patients with leprosy, myelopathies, stroke, known organ failure (hepatic, cardiac, respiratory) and exposure to industrial organic solvents.

A clinical scoring system - the United Kingdom Screening Test (UKST) [10] - was used to screen/score for symptoms of peripheral sensory neuropathy. This is a two part diagnostic test comprising a symptoms score and signs score used to determine the prevalence of peripheral neuropathy (PN) in over six thousand diabetic patients in the United Kingdom. A pretest questionnaire was developed based on the UKST symptoms score only and administered to 40 diabetic and non-diabetic patients recruited randomly from the study center to assess performance and applicability of this screening instrument for PN among Nigerian patients. All 40 (100%) subjects gave responses easily scored using the UKST symptom score. The subjects of the pretest trial were excluded from the study population proper.

Following the applicability of this screening instrument to the local population, it was administered to the cases and controls to separate those with symptoms of PN (the symptomatic population) from those without symptoms of PN (the asymptomatic population). Table 1 shows the symptoms of PN (the abnormal sensations felt by the patients in their feet/leg) scored, namely:
: Burning, numbness, or tingling, which score 2 points :Fatigue, aching or cramping, which score 1 point.The impact of site discomfort, time of worst symptoms, night time awakening and alleviating factors contributed further scores. Maximum symptoms score was 9 graded as follows:
:   Normal (no PN) 0-2
:   Mild PN   3-4
:   Moderate PN   5-6
:   Severe PN   7-9

Using this symptoms score, the criteria for symptomatic PN was presence of moderate (5-6) or severe (7-9) symptom score. These criteria were chosen to eliminate the risk of overestimation of symptomatic PN by including mild symptom scores which may be transient and also oftentimes occurs normally in the general (non-diabetic) population with increasing age. This precaution also avoids distorting the possible relationship between diabetic neuropathy and age.

Following separation of the study population into symptomatic and asymptomatic groups, the target study population the symptomatic cases and controls were further assessed with two objective instruments for testing presence of PN the UKST signs score and Bio-Thesiometry to evaluate their diagnostic performance in detecting PN among patients with symptoms of PN and thereby ascertain the objectivity or otherwise, of the symptoms of PN.

Table 2 shows the UKST signs score. The signs scored were ankle reflex, vibration, pinprick and temperature sensations. All sensations were tested at the pulp of the hallux. Vibration was assessed using a low frequency (128Hz) tuning fork [11] and temperature tested by assessing the patients' response (cold, warm or unable to tell) to iced tuning fork (tuning fork inserted in ice-blocked water for one minute) and placed on the pulp of the hallux. [8] Temperature sense was scored as abnormal if the patient perceived the iced-tuning fork as warm or unable to tell. For all sensations, each foot was scored separately. Presence of normal sensations score 0 point, while reduced/absent sensations score 1 point for each foot. Normal reflexes score 0 point, presence with reinforcement 1 point and absence 2 points for each foot.

Maximum signs score was 10, graded as follows:
:   Normal (no PN) 0-2
:   Mild PN   3-5
:   Moderate PN   6-8
:   Severe PN   9-10

Using the signs score, PN was assessed as objectively present with moderate (6-8) or severe (9-10) signs score. A kin to the symptoms score, this criteria for diagnosing PN was chosen to eliminate the risk of

overestimation by including mild signs scores that often normally occur in the general population with increasing age and potentially distorts the possible relationship between diabetic neuropathy and age [10].

Bio-Thesiometry was done using the model PVD-LP Bio-thesiometer from Bio-Medical Instrument Company Ohio, USA.[12] This instrument objectively measures vibration sensation and determines the vibration perception threshold (VPT). Patients were tested lying supine on an examination couch and prior to testing, the procedure was explained and demonstrated to the patient for familiarization. Testing was commenced by applying the vibrator of the Bio-thesiometer to the test site - the pulp of the big toe of each foot. This site is routinely used in screening tests to detect PN. [13] The vibrator was held in such a way that the weight of the vibrator furnished a standard pressure on the vibrator button with the probe balanced vertically on the pulp of the great toe.

The vibrator was held steady and the subject instructed to concentrate all attention at the test site and to verbally report the first appearance of the sensation of vibration by saying "yes". The amplitude of the vibrator button was set as low as possible at the start of testing and increased until the patient perceived vibration. The voltage on the Bio-thesiometer display at that instant was recorded as Threshold 1 (TH_1). This threshold is usually higher than the actual threshold due to the reaction time of the patient. Two further threshold readings (TH_2 and TH_3) were obtained at the test site and the mean of the last two readings used to determined the VPT for each foot.[14]

For greater reliability of the threshold readings especially when values obtained were widely divergent on the same test point, suggesting that threshold was reported by the subject when he/she thought that stimulus had been applied rather than when he/she actually felt it, catch trials were done specifically for subjects with divergent readings at the same test point. Catch trials involved turning off the main Bio-thesiometer switch without the subjects' knowledge while still applying the vibrator button. If he/she still reports sensation when stimulus had been switched off, it confirmed inappropriate response. The entire test procedure was re-explained to this category of patients to facilitate reliable cooperation and repeated.

VPT is the lowest threshold at which vibration is sensed on the pulp of the big toe and the value in normal subjects increases with age from approximately 6 volts at age 30 years to 20 volts at age 75 years [15]. Neuropathy was considered objectively present if the VPT was > 20 volts in either foot.Other physical and biochemical parameters were also documented including age (years), gender, weight (kg) and height (meters)using standiometer and blood pressure. Likewise age at first diagnosis of DM, duration of DM (years), body mass index BMI in Kg/m^2 [calculated from the weight (kg) divided by the square of the height (meters)], waist hip ratio WHR (calculated from the waist circumference WC in cm and hip circumference HC in cm). The WC was measured from halfway (midpoint) between the superior iliac crest and the lower margin of the rib cage in the mid-axillary line while the HC was measured at 1/3 of the distance between the superior iliac spine and patella.

Examination of the foot for corns, calluses and scars especially over the test sites was done and baseline fasting venous plasma glucose estimated by the glucose oxidase method and read colorimetrically in the chemical pathology laboratory of the NAUTH Nnewi. Statistical analysis was by SPSS (version 10) presenting simple descriptive statistics. The mean, standard deviation and percentages of all data were derived. The Z test was used to determine the differences between the mean ages of cases and controls and the Chi square test used to assess the relationship between gender distribution of cases and controls and diagnosis of PN by the UKST signs score and Bio-thesiometry. p value of 0.05 was taken to indicate statistical significance.Sensitivity and positive predictive values of the two methods for detecting PN was determined using appropriate formulae.[16]

RESULTS

Out of the 120 diabetic participants, 83(69.2%) had neuropathic symptoms and comprised the symptomatic case group while 10(8.3%) out of the 120 non- diabetic control group had neuropathic symptoms and comprised the symptomatic control group. Table 3 and 4 respectively show the age and sex distribution of the study participants and their clinical characteristics. The age range for the symptomatic diabetic cases was 40-78 years, and 40-59 years for the symptomatic non-diabetic control group. The difference in the mean ages of symptomatic cases (60.4 ± 9.22 years) and symptomatic controls (49.9 ± 7. 00) was statistically significant (Z = 8.82, p< 0.001). Among the cases, 53(63.9%) were males and 30(36.1%) females while the gender distribution of the controls was equal at 50.0% each. The difference in the mean fasting blood sugar (FBS) of the cases (12.9 ± 5.4 mmol/l) and controls (4.6 ± 0.5 mmol/l) was expectedly significant statistically (Z = 13.5, p< 0.001).

The difference in the mean BMI (kg/m^2) of the cases (23.65 ± 3.33) and controls (30.92 ± 3.19) was

Table 1: The United Kingdom Screening Test (Ukst): Symptom Score and Grading.

SYMPTOM	SCORE			
	1 point	2 points	Maximum	Overall
1. ABNORMAL SENSATIONS FELT:				
-Burning, Numbness or tingling	-	✓	2	
-Fatigue, Aching or Cramping	✓	-	1	
2 SITE OF DISCOMFORT				
-Feet or Soles	-	✓	2	9
-Calves	✓	-	1	
-Elsewhere	-	-	0	
3 TIME OF WORST SYMPTOMS				
-Night only	-	✓	2	
-Both day and night	✓	-	1	
-Day only/ Don't know	-	-	0	
4 ALLEVIATING FACTOR				
-Walking Around	-	✓	2	
-Standing	✓	-	1	
-Sitting, Lying or No relief	-	-	0	
5 NIGHT- TIME AWAKENING				
- Yes	✓	-	1	
- No	-	-	0	

GRADE: 0-2: (Normal) No Peripheral Neuropathy
3-4: Mild Peripheral Neuropathy
5-6 Moderate peripheral neuropathy
7-9 Severe peripheral neuropathy

Table 2: The United Kingdom Screening Test (UKST): Sign Score and Grading.

SIGN	SCORE				
	0 Point	1 point	2 points	Maximum (each foot)	Overall (both feet)
1. Ankle (Achilles tendon) reflex (with flexible tendon hammer)					
- Present	✓	-	-	0	
- Present with reinforcement	-	✓	-	1	
- Absent	-	-	✓	2	
2. Pain (Pin-Prick)					
- present	✓	-	-	0	
- Reduced or absent	-	✓	-	1	10
3. Vibration (128Hz tuning fork)					
-Present	✓	-	-	0	
-Reduced or absent	-	✓	-	1	
Temperature (ice-cold tuning fork)					
-Present (perceived as cool = normal)	✓	-	-	0	
-reduced or absent (perceived as warm or can't tell)	-	✓	-	1	

GRADE: 0-2: (Normal) No Peripheral Neuropathy
3-5 Mild Peripheral Neuropathy
6-8 Moderate peripheral neuropathy
9-10 Severe peripheral neuropathy

Table 3: Age and Sex Distribution of Symptomatic Cases and Controls.

Age group (years)	Symptomatic cases (n = 83)			Symptomatic controls (n = 10)		
	Male %	Female%	Total %	Male %	Female %	Total %
30-39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
40-49	6(11.3)	2(6.7)	8(9.6)	5(100.0)	0 (0.0)	5(50.0)
50-59	20(37.7)	14(46.7)	34(41.0)	0 (0.0)	5(100.0)	5(50.0)
60-69	14(26.4)	10(33.3)	24(28.9)	0 (0.0)	0 (0.0)	0 (0.0)
≥70	13(24.6)	4(13.3)	17(20.5)	0 (0.0)	0 (0.0)	0 (0.0)
Total	53(100.0)	30(100.0)	83(100.0)	5(100.0)	5(100.0)	10(100.0)

Table 4: Clinical Characteristics of the Participants.

Variables	Symptomatic case group n=83	Symptomatic control group n=10	Z-score	p-value
Gender (M : F)	53 : 30	5 : 5		
Mean age (years)	60.4 ±9.22	49.9 ±7.00	8.82	P<0.001
Age range (years)	40-78	40-59		
Mean FBS (mmol/L)	12.9 ±5.4	4.6 ± 0.5	13.5	P<0.001
Mean BMI (Kg/m²)	23.65 ± 3.33	30.92 ± 3.19	6.78	P<0.001
Mean WHR	0.92 ±0.089	0.96 ±0.068	1.69	P>0.05

Table 5: Comparison of Diagnostic Performances of UKST (Signs Score) and Bio-Thesiometry in Detecting PN.

Diagnostic Methods	Symptomatic Cases		Total	Symptomatic Controls		Total
	+	-		+	-	
UKST	74	9	83	10	0	10
BIO-TH	59	24	83	5	5	10
Total	133	33	166	15	5	20

X^2 of the two method in detecting PN in symptomatic cases = 8.51, df = 1, P<0.01
X^2 of the two method in detecting PN in symptomatic controls = 4.27, df = 1, P< 0.05
(using continuity correction factor)

Comparison of symptomatic cases and controls:
X^2 = 0.68, df =1, P> 0.3
Key:
PN = Peripheral Neuropathy
UKST = United Kingdom Screening Test (Signs score)
BIO-TH = Bio-thesiometry

Table 6: Sensitivity and Positive Predictive Values of theTwo Methods of Diagnosing PN.

Method of diagnosis	Peripheral neuropathy		Sensitivity %	Positive predictive value (%)
UKST	Symptomatic cases n = 83	Symptomatic controls n = 10		
Positive	74	10		
Negative	9	0	89.2%	88.1%
BIO-TH				
Positive	59	5	71.1%	92.2%
Negative	24	5		

Statistically significant (Z = 6.78, p < 0.001) but not so in the mean WHR (0.92 ± 0.089 vs. 0.96 ± 0.068, Z =1.69, p >0.05). Table 5 compares the diagnostic performances of the UKST and Bio-thesiometer in detecting PN among the symptomatic cases and controls. Among the cases, UKST detected PN in 89.2% (74/83) compared to Bio-TH (71.1%; 59/83), the difference in the ability of the two methods to detect PN in this group being statistically significant (X^2 = 8.51, df = 1, p<0.01). Among the controls, UKST detected PN in 100.0% (10/10) compared to Bio-thesiometry (50.0%; 5/10), the difference in the ability of the two methods to detect PN in this group also being statistically significant (X^2 = 4.27, df =1 p <0.05, using continuity correction factor). The difference in the ability of both methods to detect PN between the cases and controls was however not statistically significant (X^2 = 0.68, df = 1, p>0.3).

Table 6 shows the sensitivity and positive predictive value patterns of both methods of diagnosing PN among the cases and controls. The UKST was more sensitive compared to Bio-thesiometer (89.2% vs 71.1%) but Bio-thesiometry had a better positive predictive value (92.2% vs 88.1%) for detecting peripheral neuropathy.

DISCUSSION

Peripheral nerve damage is a common complication of diabetes [17] and leads to a variety of clinical syndromes the diabetic neuropathies.[18] These consist of somatic and or autonomic features. Somatic complications may be motor, sensory or mixed, symmetrical (typical glove and stocking distribution) or asymmetrical (mononeuropathy or polyneuropathy), affecting the most distal parts of the longest nerves first.[3] The importance of peripheral neuropathy (PN) complicating diabetes mellitus (DM) cannot be overemphasized. In Western countries, consensus opinion is that PN is one of the commonest risk factors for foot ulceration in patients with diabetes [19,20] and has variously been reported as occurring in 5-80%.[10,21] Data from sub-Saharan Africa equally report that foot disease in diabetes is more likely due to PN rather than to peripheral vascular disease.[22]

PN is detected by screening for typical symptoms and signs but presence of symptoms however do not always indicate underlying neuropathy and vice versa.[6] In addition, accurate assessment of symptoms is known to be difficult and poorly reproducible with significant differences in judging symptom severity occurring even among highly trained neurologists. [23] This study therefore sought to determine the objectivity of the symptoms of diabetic PN by first using a gold standard the United Kingdom Screening Test (UKST) symptoms score to objectively screen a population of diabetic cases and non-diabetic controls. Those cases and controls with objective symptoms of PN using the UKST symptoms score were selected and the objectivity of their neuropathic symptoms further tested with two methods- the UKST signs score and Bio-Thesiometry (Bio-TH) to evaluate the diagnostic performance of these two methods in detecting and confirming the presence of PN in the study population. This is a pioneering study as no study using these research tools on Nigerian diabetic patients has been reported to date.

The UKST [10] is a two part diagnostic test and was used by Young et al to determine the prevalence of PN in over six thousand diabetic patients in the United Kingdom. Table 1 shows the symptoms of PN scored, the maximum symptom score being 9 and graded as normal (no PN), mild, moderate and severe PN. Using the symptom score, the criteria for symptomatic PN for this study was the presence of moderate (5-6) or severe (7-9) symptom scores and this criteria was chosen to eliminate the risk of overestimating symptomatic PN by including mild symptom scores. Mild symptom scores may be transient and oftentimes also occurs normally in the general (non-diabetic) population with increasing age. Using the symptoms score, 69.2% (83/120) of the diabetic participants and 8.3% (10/120) of the non-diabetic participants had symptomatic PN and comprised the case/control study population respectively.

Table 2 shows the signs of PN scored, the maximum sign score being 10 and similarly graded as normal (no PN), mild, moderate and severe PN. Using the signs score, PN was assessed to be objectively present with moderate (6-8) or severe (9-10) signs scores, a criteria chosen akin to symptom score grades to eliminate the risk of overestimating PN by including mild signs scores, which may also be found in the general population especially with advancing age. Using the signs score, this study showed that the symptoms of PN in both cases and controls were objective. 89.2% (74/83) of the symptomatic diabetic cases and 100.0% (10/10) of the symptomatic non-diabetic control group were found to have PN using the UKST signs score.

Bio-thesiometry screens for vibration sensation and is an objective, rapid and reliable test for PN.[12] The Bio-thesiometer is essentially an electronic tuning fork designed to measure simply and accurately the threshold of appreciation of vibration in human Subjects. The device allows vibration sensation to be adjusted up or down depending on the voltage applied, to determine the vibration perception threshold (VPT) with a high degree of accuracy. VPT is defined as the lowest voltage at which vibration can be sensed on the pulp of the big toe and the value in normal subjects increases with age from approximately 6 volts at age 30 years to 20 volts at age 75 years.[15] Raised VPT has been reported as one of the first signs in peripheral nerve disorders such as polyneuropathy and nerve entrapment [24] and is thought to be neuro-selective for large fibre function.[25] A major advantage of screening with the Bio-thesiometer apart from detecting PN, is the

possibility to predict those diabetic patients at increased risk of foot ulceration. A prospective trial of 469 diabetic patients with no history of foot ulceration found the VPT an excellent predictor of future foot ulceration.[14] This trial showed that VPT >25 volts is strongly associated with the risk of foot ulceration and carries a seven fold risk of foot ulceration compared to those with a VPT <15 volts. It also showed that less than 4 percent of patients with a VPT< 25 volts developed new ulcers unlike almost 20 percent of those with a VPT > 25 volts. A number of epidemiological surveys of neuropathy [8,10] have additionally shown that measurements of VPTs correlate with clinical scoring systems.

In our study, symptomatic PN was considered objectively present if the VPT was >20 volts in either foot, and Bio-thesiometry detected PN in 71.1% (59/83) and 50.0% (5/10) of the symptomatic cases and controls respectively. This high proportion of positive detection of PN by Bio-thesiometry among the symptomatic diabetic cases, akin to the UKST signs scores findings, shows that the symptoms of PN in Nigerian diabetic patients are objective and genuinely indicate presence of PN. Though the UKST was more sensitive than Bio-thesiometry (89.2% vs 71.1%) in detecting the presence of PN, Bio-thesiometry had a better (92.2% vs 88.1%) positive predictive value, in agreement with previous studies, of predicting those at increased risk of foot ulceration from PN.

However while the Bio-thesiometer readily makes a diagnosis of significant sensory disturbance, it has some limitations as some factors may affect the threshold of perception of vibration and yet are not pathological. Age in particular influences vibration perception and in the normal population, VPT increases with age.[26] Threshold is lower in children and young adults compared to adults over 50 years and this increase in threshold with age is especially true in the lower extremities.[27,28]

CONCLUSION
This study has shown that the symptoms of peripheral neuropathy (PN) among Nigerian diabetic subjects when evaluated with a gold standard (the United Kingdom Screening Test- symptom score), are real, objective and significant.Scoring the symptoms of PN using this gold standard for diabetic patients presenting to the medical outpatient department and diabetic clinics should be a minimum requirement to detect early those patients with significant PN (moderate to severe UKST symptom scores). Scoring these symptoms is minimally time consuming (unlike scoring the signs) and can be accommodated in most clinics handling diabetic patients, no matter how busy. It is also without cost, compared to the costly and unavailable Bio-thesiometer and therefore very handy in our technologically and economically handicapped Society. Loss of limbs to diabetes, oftentimes from PN remains an intractable problem. Using this simple and cost effective symptom scoring system will help "target" foot care and foot education efforts to the population at most risk and most likely to benefit from early preventive efforts as effective prevention of diabetic foot problems, especially ulceration, through education and other preventive strategies is time consuming and expensive. [29-31] Identifying appropriate "at risk" groups [32] improves the effectiveness of foot care programs towards achieving the goal of the St Vincent Declaration and target of reduction in the appalling toll of limb loss to diabetes.

Larger scale studies using this gold standard among the Nigerian diabetic population is recommended to further evaluate the efficacy of this instrument in effectively assessing symptomatic diabetic peripheral neuropathy.

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