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DIABETIC SENSORY NEUROPATHY: A REVIEW OF THE LITERATURE

[1]Oguejiofor O.C, [2]Omejua E.G, [1]Ezejiofor O.I* and [1]Odenigbo U.C

[1]Department of Medicine, Nnamdi Azikiwe University Awka.
[2]Department of Medicine, Federal Medical Centre Owerri.

***Corresponding Author: Dr. Ezejiofor O.I**

Department of Medicine, Nnamdi Azikiwe University Awka.

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ABSTRACT

Background and objective: Involvement of the peripheral nerves is the most common and certainly the most troubling chronic complication of diabetes mellitus. World wide, diabetic peripheral neuropathy is the most common type of neuropathy, with diabetic sensory neuropathy being the commonest variant and the most important risk factor for foot ulceration and limb loss among diabetic subjects. It presents with a gamut of often bizarre symptomatology and is poorly responsive to pharmacological interventions. This article reviews the literature on this very important risk factor for diabetic foot disease. **Method:** Research works on current classification, pathogenesis, clinical presentation and more importantly, assessment models for diagnosing sensory neuropathy, were reviewed. The complications and the various treatment options- pharmacological and non-pharmacological- were also explored. **Results and conclusion:** Advances in the methods for evaluating and diagnosing sensory neuropathy in diabetes mellitus presents huge opportunities and potentials for improved objective assessment of the gamut of bizarre symptomatology of diabetic sensory neuropathy. This article will hopefully generate interest in further local researches on this subject using these assessment models, to determine the pattern of presentation of symptoms of sensory neuropathy among Nigerian diabetic subjects.

KEYWORDS: Diabetes mellitus, Diabetic peripheral neuropathy, Diabetic sensory neuropathy.

INTRODUCTION

The most detailed acceptable definition of diabetic neuropathy (DN) as agreed upon at the 1988 San Antonio Conference on Diabetic Neuropathy states that " DN is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy"[1] Involvement of the peripheral nerves is probably the most common and certainly the most troubling chronic complication of diabetes.[2]

Peripheral neuropathies have been described in patients with primary (types 1 and 2) and secondary diabetes of diverse causes, suggesting a common etiologic mechanism based on chronic hyperglycemia.[2]

In both types 1 and 2 diabetes the prevalence of diabetic peripheral neuropathy varies with severity and duration of hyperglycemia[3] The importance of hyperglycemia in the pathogenesis of neuropathy in type i diabetes mellitus was demonstrated in the Diabetes Control and Complications Trial [DCCT] This landmark study showed that strict glycaemic control decreased the incidence and slowed the progression of diabetic neuropathy.[3]

EPIDEMIOLOGY

Diabetic peripheral neuropathy (DPN) is the most common neuropathy in the western world. Clinical or subclinical neuropathy has been estimated to occur in 10-100% of diabetic patients depending on the diagnostic criteria used and patient populations examined[4] While no definite racial predilection has been demonstrated for diabetic neuropathy, male subjects usually have a higher incidence of diabetic neuropathy than females. Diabetic neuropathy occurs at any age The duration-corrected prevalence and incidence rates of neuropathy does not "differ significantly with age but symptomatic presentation is most common in patients older than 50 years, reflecting a link with duration of hyperglycemia rather than age[4]

CLASSIFICATION

The Consensus Panel report and recommendations of the San Antonio Conference on diabetic neuropathy[1] classified diabetic neuropathy into two major classes.

CLASS I: SUBCLINICAL NEUROPATHY comprising

(a) Abnormal electrodiagnostic tests' (EDX)
-decreased nerve conduction velocity.
-decreased amplitude of evoked potential or nerve action potential.
(b) Abnormal Quantitative Sensory Testing (QST)

-vibratory/tactile -thermal warming/cooling -other
(c) Abnormal autonomic function tests (AFT)
-diminished sinus arrhythmia -diminished sudomotor function -increased pupillary latency.

•CLASS II: CLINICAL NEUROPATHY comprising:
(a) Distal Symmetric sensorimotor polyneuropathy
-primarily small fibre neuropathy -primarily large fibre neuropathy -mixed
(b) Autonomic neuropathy
(c) Focal neuropathy

PATHOGENES1S
The pathogenesis of diabetic neuropathy is poorly understood but many theories exist. Currently, seven mechanisms are thought to contribute to the pathogenesis, but in contrast to previous years when they were regarded as operating independently, these mechanisms most probably interact in a complex manner.[5]

THE METABOLIC THEORY
This theory proposes that hyperglycemia causes increased levels of intracellular glucose in nerves, leading to saturation of the glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced nerve myoinositol, decreased membrane Na^+/K^+ATPase activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation. This is the rationale for the use of aldose reductase inhibitors to improve nerve conduction.

VASCULAR (ISCHAEMIC-HYPOXIC) THEORY:
According to this theory, endoneural ischemia develops because of increased endoneural **vascular** resistance to hyperglycemic blood. Various metabolic factors, including formation of advanced glycosylation end products, also have been implicated. The end results are capillary damage, inhibition of axonal transport, reduced Na^+/K^+ATPase activity, and finally axonal degeneration. Endoneural microvascular deficits with subsequent ischemia and hypoxia leads to generation of reactive oxygen species (oxidative stress) and the so-called hyperglycaemic pseudohypoxia.

ALTERED NEUROTROPHIC SUPPORT THEORY postulates that deficits in neurotrophism leads to reduced expression and depletion of neurotrophic factors such as nerve growth factor (NGF), neuratrophin-3 and insulin-like growth factor, as well as alterations in axonal transport.[6]

AUTOIMMUNE THEORY
Autoimmune diabetic neuropathy is postulated to result from immunogenic alteration of endothelial capillary cells. Generation of autoantibodies to nerves, as well as inflammatory changes occur. This is the basis for the use of intravenous immunoglobulin (IV Ig) to treat some variants of DM neuropathy[7]

INCREASED ACTIVITY OF PROTEIN KINASE C *B* (PKC *B*)
According to this theory, hyperglycemia-induced synthesis of diacylglycerol (DAG) from increased breakdown of fats results in activation of PKC beta, which appears to mediate changes in nerve structure and microvasculature[8]

ACCUMULATION OF NON-ENZYMATIC ADVANCED GLYCATION END-PRODUCTS (AGES) on nerve and/or vessel proteins, which leads to endothelial dysfunction, impaired nerve blood flow and ischemia[9-11]

DISTURBANCES *IN N-6* ESSENTIAL FATTY ACID AND PROSTAGLANDIN METABOLISM: This results in alterations of nerve membrane structure with microvascular and haemorrheological abnormalities.

ADDITIONAL FACTORS IN SENSORY NEUROPATHY
Additional sources of sensory neuropathy in patients with diabetes mellitus (DM) includes
- neurotoxic medications (examples include Isoniazid, high dose pyridoxine)
- alcohol abuse
- B12 deficiency
- renal disease
- abnormally low levels of vitamin B6 or B1
- monoclonal gammopathy and hypertriglyceridaemia

Studies have shown that 25% of diabetic subjects have more than one additional cause[12] and these subjects more often have sensory symptoms and findings in the hands.[13]

CLINICAL PRESENTATION
The clinical manifestations of sensory neuropathy in diabetes may be grouped as “positive" symptoms or "negative" symptoms.

"POSITIVE" symptoms comprise
- Paraesthesiae
- Pain: burning; stabbing, pinprick, lancinating, shooting
- Crawling sensations
- Electric shock-like feelings
- Allodynia/hyperesthesia (hypersensitivity to touch)

"NEGATIVE" symptoms comprise
- Numbness or "deadness" (akin to wearing gloves or socks
- Loss of balance (especially in the dark)
- Painless ulcers

A. Distal symmetric polyneuropathy (DSP)
This is the most common manifestation of diabetic neuropathy, with multiple nerves being affected distally and symmetrically[14] Symptoms affect peripheral nerves in a length-dependent pattern (the longest nerves are affected first). Sensory abnormalities predominate and

commonly present as painful paresthesias and numbness These begin in the toes and ascend proximally in a stocking-like distribution over months and years in established cases. It is often unrecognized in its earliest stages. Early clinical signs are loss of vibration sense, pain sensation (deep before superficial) and temperature sensation in the feet[1,4] At later stages, feeling of 'walking on cotton wool or mud[1] with loss of balance especially in the dark occur. Involvement of the hands is much less common compared to the feet. When sensory symptoms reach the knees, hands develop similar symptoms, progressing proximally in a glove-like distribution. Anterior aspect of the trunk and vertex of the head may be affected at a very late stage. The 'Stocking and Glove' sensory loss denotes the involvement of the feet and hands by DSP.

B. Acute Painful Neuropathy

This is less common than DSP. The patient describes burning or crawling pains in the feet, shins and anterior thighs. These are typically worse at night and pressure from bedclothes may be intolerable (allodynia).

It may present after sudden improvement in glycaemic control and spontaneous remission after 3-12 months is usual if good glycaemic control is maintained. A more chronic form of painful neuropathy develops later in the course of the disease and is sometimes resistant to most forms of therapy. It is increasingly recognized that positive neuropathy sensory symptoms are separate phenomena from negative symptoms[15] Thus, for some patients with onset of polyneuropathy, positive symptoms may predominate without or with only a few neuropathic findings. Later, as positive neuropathic sensory symptoms abate, negative symptoms and impairments may become evident and worsen.

Also, these positive sensory symptoms may be more bothersome than negative neuropathic sensory symptoms, may inspire patients seeking relief from pain to visit physicians, and may be more debilitating (interfering with meeting, work, family, and social responsibilities) than negative symptoms or impairments. These positive neuropathic symptoms are thought to be due to small-fiber sensory nerve fiber involvement.

PHYSICAL EXAMINATION includes assessing for

- Loss of or diminished vibration sensation (with low frequency 128Hz tuning fork)
- Joint Position (JP) Sensation
- Pin-prick
- Light touch ,
- Temperature
- Pressure perception (with Quantitative sensory monofilament/Aesthesiometer)

ASSESSMENT MODELS FOR SENSORY NEUROPATHY:

1. THE UNITED KINGDOM SCREENING TEST (UKST).

This is a 2-part diagnostic test[16] consisting of a simple symptom score and physical examination score.

A. UKST SYMPTOM SCORE (see table 1): Symptoms are evaluated and scored as follows:

(a) What is the sensation felt?

- burning, numbness, or tingling in the feet (2 points)
- fatigue, cramping, or aching (1 point)
- Maximum *2* points

(b) What is the location of symptoms?

- Feet (2 points). Calves (1 point); elsewhere (no point); maximum is 2 points

(c) Have the symptoms ever woken patient at night?

- Yes (1 point). No (no point)

(d) What is the timing of symptoms?

- Worse at night (2 points)
- Present day and night (I point)
- Present only during the day (no point)
- Maximum is 2 point

(e) How are symptoms relieved?

- Walking around (2 points);
- Standing (I point)
- Sitting or lying or no relief (no point)
- Maximum is 2 points

Total symptom score: 9

- 0-2 = normal
- 3-4 = mild neuropathy
- 5-6 = moderate neuropathy
- 7-9 = severe neuropathy

B. UKST 'SIGN' SCORE (see table 2)

This is a quantitative score for physical findings and comprises

(a) What is the Achilles tendon reflex?

- Absent (2 point for each foot)
- Present with reinforcement (1 point for each foot)

(b) What is the vibration sense?

« Absent or reduced (1 point for each foot)

(c) What is the pin-prick sensation?

- Absent or reduced (I point for each foot)

(d) What is the temperature sensation?

- Reduced (1 point for each foot)

THE TOTAL NEUROLOGICAL SIGNS **SCORE is 10, graded as**

- 0-2 = normal
- 3-5 = mild neuropathy
- 6-8 = moderate neuropathy
- 9-10 = severe neuropathy

Peripheral neuropathy is considered to be present if there are moderate or severe signs (≥6) even in the absence of symptoms, or if there are at least mild signs (≥3) in the presence of moderate symptoms (≥5).

• A sign score of ≥ 8 indicates high risk for foot ulceration.

2. Clinical stratification method using the Toronto Clinical Neuropathy Score[17]

Clinical parameters are stratified and scored as shown:

▪ *Symptom scores*	*Reflex scores*	*Sensory test scores*
•Foot pain	Knee reflexes	Pinprick
•Numbness	Ankle reflexes	Temperature
•Tingling		Light touch
•Weakness		Vibration
•Ataxia		Position sense
• Upper limb symptoms		

•Symptom scores are graded as present = 1, absent = 0 (numbness, tingling as perceived at toes and in feet)
•Reflex scores are graded as absent = 2, reduced = 1, normal = 0 for each side.
•Sensory test scores are graded as abnormal - 1, normal = 0.
•Maximum possible score is 19.
•The score is used to stratify patients into three groups of severity; 6-8 indicate mild neuropathy, 9-11 indicate moderate neuropathy, and >12 indicate severe neuropathy.

OTHER FORMS OF ASSESSMENT **OF SENSORY NEUROPATHY IN DM**

1. The NTSS-6 [Neuropathy Total Symptom Score-6] questionnaire

This instrument was developed to evaluate the frequency and intensity of individual neuropathy sensory symptoms identified frequently by patients with DPN (including numbness and/or insensitivity; prickling and/or tingling sensation; burning sensation; aching pain and/or tightness; sharp, shooting, lancinating pain; and allodynia and/or hyperalgesia)[12] The NTSS-6 provided a valid assessment of neuropathy sensory symptoms in patients with DM and DPN, which suggests that it may be useful for symptom evaluation in clinical trials and practice[12]

2. The 10-g Semmes-Weinstein monofilament test (Aesthesiometry)- is a sensitive,
specific, simple, and inexpensive screening tool for identifying diabetic peripheral neuropathy in clinical setting[13]

Although a number of different techniques for monofilament testing exist, this technique has been validated as a reliable screening test for the diagnosis of diabetic neuropathy.[14]

3. Quantitative sensory threshold [QST] testing

These are important noninvasive tools in diabetic sensory neuropathy assessment commonly used in clinical trials [20-23] QST assesses individual sensory modalities, including the perception thresholds for vibration and thermal stimuli.

(i) Vibration Perception Threshold [VPT] testing /Bio-thesiometry- This is the quantitative modality most commonly used for assessment of diabetic sensory polyneuropathy.[17,23]
(ii) Cooling detection threshold is equivalent to other modalities of quantitative sensory threshold testing.[17]

4. Intra-epidermal nerve fiber analysis of skin biopsy. This is regarded as the reference standard for the identification of small-fiber neuropathies.[17]

5. Nerve conduction studies (abnormality in two or more nerves). These remain the most reliable, accurate, and sensitive measure of peripheral nerve function.[24] However, the technique assesses the function of large-caliber nerve fibers exclusively. The earliest finding is distal slowing of conduction with relative preservation of proximal nerve conduction velocities. They correlate with morphologic findings on nerve biopsy.[7]

In human neuropathies, it is common clinical experience that improvement or recovery of nerve conduction may lag well behind clinical improvement.[15] Thus, in the Diabetes Control and Complications Trial (DCCT), a statistically significant difference in nerve conduction was not recognized until several years had elapsed.[3, 25] The recent introduction of computer-assisted programs for the measurement of sensory modalities for clinical trials has been a major advance.[26] Due to their invasive nature and associated morbidity, nerve biopsy studies are no longer used in clinical trials.[26] Recently, using magnetic resonance imaging [MRI], significant spinal cord atrophy has been demonstrated in established neuropathy. If this observation proves to be an early feature, then a relatively rapid, noninvasive MRI technique may be used in the future to characterize diabetic neuropathy.[15, 26]

DIAGNOSIS

Proposals tor the minimal criteria for the diagnosis of diabetic polyneuropathy include

- ❖ ≥2 abnormal evaluations from among
- (I) neuropathic symptoms,
- (2) neuropathic deficits,
- (3)Nerve conduction velocity
- (4) quantitative sensory examination [QSE], and
- (5)QAE
- ❖ One of the two must include abnormality of NC or QAE (DB or VAL)[18]

DIFFERENTIAL DIAGNOSIS

It is important to exclude other possible causes of sensory neuropathy as soon as the
clinical or subclinical suspicion of sensory neuropathy is entertained in subjects with DM,
as up to 10% of DM patients may have other causes for their neuropathy.[13, 27]
Important differential diagnoses include.

- ▪ Metabolic disorders
- ▪ Toxic etiologies
- ▪ Infections and inflammatory disorders
- ▪ Others

It is important to recognize these etiologies because most are treatable

COMPLICATIONS OF DIABETIC SENSORY NEUROPATHY

The clinical impact/implications of diabetic sensory neuropathy is formidable. It is a major risk factor for foot trauma and ulceration and is responsible for 50-75% of nontraumatic amputations.[28] Pain associated with diabetic neuropathy has a substantial impact on the quality of life, particularly interfering with sleep and enjoyment of life[29, 30], especially in patients with suboptimal pain management.[31] Diabetic neuropathic cachexia is an uncommon complication of painful sensory neuropathy seen mainly in elderly male subjects and is associated with depression, consequent anorexia and undernutrition Regarding mortality, there is accumulating evidence suggesting that markers of polyneuropathy such as impaired nerve conduction velocity (NCV) and vibration perception threshold (VPT) predict mortality in diabetic patients.[32,33]

TREATMENT

Improvement of sensory symptoms and quality of life[34] is recognized as an important clinical endpoint, particularly if there is improved nerve function. The Ad Hoc Panel on Endpoints for Diabetic Neuropathy Trials has recommended that the effectiveness of potential agent for DPN treatment meet 3 criteria.[30]

(1) The agent should reduce neuropathic sensory symptoms to a statistically significant degree
(2) Improvements should not be related to worsening of neuropathy, and
(3) The agent should result in clinically meaningful improvements in neuropathic sensory symptoms.[35]

There are 3 aspects to be considered in the treatment of diabetic sensory neuropathy

(1) control of blood sugar and other risk factors
(2) modulation of the pathogenetic metabolic disorders ("'ancillary therapies")
(3) symptomatic treatment of sensory neuropathy

CONTROL OF BLOOD SUGAR AND OTHER RISK FACTORS

The DCCT and Kushimoto studies have clearly demonstrated the value and benefit of strict glycemic control on onset and progression of diabetic neuropathy[3]

ANCILLARY THERAPIES

Ancillary therapies aim to modulate pathogenic metabolic disorders contributing to the development of DPN, and therapies currently under consideration include.

- aldose reductase inhibitors[36],
- myo-inositol[37],
- essential fatty acids[38,39],
- vitamins,
- protein kinase C inhibitors,
- vasodilators[40],
- antiprostaglandins[41],
- nerve growth factors[42],
- ACE inhibitors,
- advanced glycation end product inhibitors (example aminoguanidine)[43],
- acetyl-L-carnitine[44], and
- Antioxidants example alpha -lipoic acid (ALA)[45]

SYMPTOMATIC TREATMENT OF DLABET1C SENSORY NEUROPATHY

Symptomatic pharmacological treatment of chronic painful diabetic neuropathy remains a challenge. The agents that have been shown to be useful include

ANTIDEPRESSANTS

These may act by altering central perception of pain rather than by antidepressant effect (the latter effect appears later and at higher doses). Several authors consider the Tricyclic Antidepressants (TCAs) to be the drug treatment of choice for neuropathic pain. However, their use is limited by relatively high rates of adverse events and several contraindications. Common agents in use include

- Amitryptiline 50-150mg at night (oral)
- Nortriptylline 50-150'mg at night (oral)
- Imipramine lOOmg qds (oral)
- Paroxetine 40mg qds (oral)

The slow serotonin reuptake inhibitors [SSRIs] have been found to be less effective than TCAs. Recent interest has focused on antidepressants with dual selective inhibition of serotonin and noradrenaline, such as venlafaxine and duloxetine. The effect of venlafaxine (150-225 mg) is attributed to an analgesic, rather than antidepressant effect.[46]

In a recent trial, venlafaxine was as effective as imipramine in reducing neuropathic pain, but tolerability was more favourable with venlafaxine[47]

Although duloxetine has not been formally compared with TCAs, the rates of adverse effects appear to be lower. Both venlafaxine and duloxetine have not yet been licensed for the treatment of neuropathic pain.

ANTICONVULSANTS

Agents currently in use include

(1) Carbamazepine (200- 800mg/d)
(2) Phenytoin (100-300mg/d)
(3) Na Valproate (1000-3000mg/d)
(4) Gabapentin (300- 1200mg/d) is structurally related to GABA that plays a role in pain transmission and modulation. Mean pain score and global pain score data indicate no significant difference between gabapentin and amitriptyline.[48] The exact mechanisms of action of this drug in neuropathic pain are not fully elucidated. Mechanism may involve high affinity binding to the 2-subunit of voltage-activated calcium channels.
(5) Pregabalin is another 2- ligand with a 6-fold higher binding affinity than gabapentin. Two large phase III trials

have shown that pregabalin is effective in painful diabetic neuropathy.[49]

STRONG OPIOIDS FOR ADD-ON TREATMENT

Two recent trials have demonstrated significant pain relief and improvement in quality of life following treatment with controlled-release oxycodone (10-30mg/d), in patients with painful diabetic neuropathy whose pain was not controlled adequately on standard treatment with antidepressants and anticonvulsants.[50,51]

However, chronic use of narcotics should be avoided because of the abuse potential and development of tolerance.

OTHER MEDICATIONS

(1) Fluphenazine 1mg tds (oral)
(2) Mexiletine 150-600mg/d qds (oral)
(3) Capsaicin 0.25-0.75% qds (topical)-Acts by depletion of substance P in neurons
(4) NSAIDS

-Ibuprofen 600mg qds
-Sulindac 200mg bd

HOW SUCCESSFUL IS DRUG TREATMENT OF SENSORY NEUROPATHY IN DM?

A survey of physicians experienced in treating neuropathic pain demonstrated that only a minority would rate results of analgesic treatment as excellent or good using

- antidepressants *(40%)*,
- anticonvulsants (35%),
- opioids (30%) or
- simple analgesics (18%) [52]

Studies have shown greater improvements after treatment in patients with early neuropathy than in more advanced cases. One study found that treating patients based on the categorization of their neuropathic pain by symptoms and pathogenesis resulted in improvement in more than 87% of subjects.[53]

Superficial pain, often described as "burning" or "sunburn-like tingling," responds well to topical agents, such as capsaicin cream (0.25-0.75%) applied four times a day to the dysesthetic areas[54] Deep pain, described as "pins and needles" or "sharp and stabbing," generally responds well to gabapentin or tricyclic medications (especially imipramine, amitriptyline, and desipramine).[54] In refractory cases, tricyclic drugs may be combined with oral mexiletine or a local anesthetic (e.g., lidocaine).[54]

NON-PHARMACOLOGICAL TREATMENTS

Lack of entirely satisfactory pharmacotherapy of painful diabetic neuropathy have prompted trial of non pharmacologic options including.

Psychological support to shore up subjects moral through education and optimistic support, as debilitating neuropathic pain often improves spontaneously within months.

Cognitive Behavioural Therapy (example coping skills)

Massage therapy[55]

Transcutaneous electrical nerve stimulation

Acupuncture

Physical measures (example cold water immersion) have all been tried Recently, treatment with a monochromatic near-infrared medical device[56] and wearing of shoe insoles generating a static magnetic field (450 G)[57] have been shown to reduce neuropathic pain in diabetic patients. Further studies are needed to confirm these promising results.

Table 1: The united kingdom screening test (ukst). Symptom score and grading.

SYMPTOM	SCORE			
	1 Point	2 Point	Maximum	Overall
1. ABNORMAL SENSATIONS FELT				9
-Burning, Numbness or tingling	-	√	2	
-Fatigue, Aching or Cramping	√	-	1	
2. SITE OF DISCOMFORT -Feet or Soles	-	√	2	
-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 AWAKEING -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 Points	2 Points	Maximum (each foot)	Overall (both feet)
1. Ankle (Achilles tendon) reflex (with flexible tendon hammer)					10
-Present	√	-	-	0	
-Present with reinforcement	-	√	-	1	
-Absent	-	-	-	2	
2. Pain (Pin-Prick) -Present	√	-	-	0	
-Reduced or absent	-	√	-	1	
3. Vibration (128Hz tuning fork)					
-Present	√	-	-	0	
-Reduced or absent	-	√	-	1	
4. 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

CONCLUSION

Diabetic sensory neuropathy is one of the most chronic and troubling complications of diabetes mellitus, with often poor response to pharmacological interventions. It is the commonest risk factor for foot ulceration and limb loss among diabetic subjects. The gamut of bizarre symptomatology, both positive and negative, necessitated a review of the literature of this very important clinical state. Hopefully, it will generate interest in original local researches around this condition, especially to determine the pattern of presentation of symptoms of sensory neuropathy among Nigerian diabetic subjects.

REFERENCES

1 Consensus Panel Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy. *Diabetes.*, 1988; 37: 1000
2 Greene DA, Feldman EL, Stevens MJ et al. Diabetic neuropathy. In: Porte D Jr, Sherwin R, eds. *Diabetes mellitus.* East Norwalk, CT: Appleton & Lange, 1997; 1009
3 DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl J of Med.*, 1993; 329: 977-986.
4 England JD, Gronseth GS, Franklin G et al Distal symmetric polyneuropathy: a definition for clinical research, report of the American Academy of Neurology and the American Association of Electrodiagnostic Medical and the American Academy of Physical Medicine and Rehabilitation *Neurology.*, 2005; 64(2): 199-204
5 Cameron NE, Eaton SE, Cotter MA, Tesfaye S Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia.*, 2001; 44: 1973-1988[CrossRef)[lSI][Medline]
6 Tomlinson DR, Fernyhough P, Diemel LT Role of neurotrophins in diabetic neuropathy and treatment with nerve growth factors. *Diabetes.*, 1997; 46(suppl2): V S43-S49.
7 Younger DS, Rosoklija G, Hays AP, Trojaborg W, Latov N Diabetic peripheral neuropathy a clinicopalhoiogic and immunohistochemical analysis of sural nerve biopsies. *Muscle Nenve.*, 1996; 19: 722-727, [Medline]
8 Ways DK, Sheetz MJ The role of protein kinase C in the development of the complications of diabetes. *1'itarn Harm.*, 2000; 60: 149-193. Abstract
9 Feldman EL, Stevens MJ, Greene DA Pathogenesis of diabetic neuropathy. *Clin Nenrosci.*, 1997; 4: 365.
10 Greene DA, Stevens MJ, Obrosova I, Feldman EL Glucose-induced oxidative stress and programmed cell death in diabetic neuropathy. *Ear J Pharmacol.*, 1999; 375 217.
11 Zochodne DW Diabetic Neuropathies features and mechanisms. *Brain Puthol.*, 1999; 9: 369.
12 The MBBQ Study group. Development and validity testing of the neuropathy total symptom score-6 questionnaire tor the study of sensory symptoms of diabetic peripheral neuropathy *Clin Ther* Aug., 2005; 27(8): 1278-94.
13 Gorson KC, Ropper AH Additional causes for distal sensory polyneuropathy in diabetic patients. *Journal of Neurology, Neurosurgery and Psychiatry.*, 2006; 77: doi: 10 1 L36/jnnp.2005 075 V19
14 Ugoya SO, Echejoh GO, Ugoya TA et al Clinically Diagnosed Diabetic Neuropathy: Frequency, Types and Severity *J Nail Meet Assoc.*, 2006; 98: 1763-1766.
15 The SYDNEY Trial Study Group The Sensory Symptoms of Diabetic Polyneuropathy Are Improved With -Lipoic Acid Diabetes *Care., 2003;* 26: 770-776.

16 Young MJ, Boulton AIM, Macleod AF et al: A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population *Diabetologia., 1993 [Medline];* 36: 150-154.
17 Zinman LH, Bril V, Perkins BA Cooling Detection Thresholds in the Assessment of Diabetic Sensory Polyneuropathy Comparison of CASE IV and Medoc instruments *Diabetes Care., 2004;* 27: 1674-1679.
18 Lee S, Kim H, Choi S et al Clinical usefulness of the two-site Semmes-Weinstein monofilameut test for detecting diabetic peripheral neuropathy *J Korean Med Sci.,* 2003 Feb; 18(1): 103-7.
19 Perkins BA, Olaleye D, Zinman B, Bril V Simple screening tests for peripheral neuropathy in the diabetes clinic *Diabetes ('are., 2001*[Abstract/Free Full Text]; 24: 250-256.
20 Kahn R Proceedings of a consensus development conference on standardized measures in diabetic neuropathy: quantitative sensory testing. *Diabetes ('are* 1 992 [Medline] 15: 1092-1094
22 Maser R, Nielsen V, Bass E et al: Measuring diabetic neuropathy: assessment and comparison of clinical examination and quantitative sensory testing *Diabetes* (*'arc* 1989[Abstract]; 12: 270-275
23 Bril V Peripheral neuropathies: experience in large multicentre trials In *Clinical Trials in Neurology*. Guiloff R, Ed. London, Springer-Verlag, 2001; 479-484.
24 Dyck P, Bushek W, Spring E et al: Vibratory and cooling detection thresholds compared with other tests in diagnosing and staging diabetic neuropathy, *Diabetes Care 1987 [Abstract];* 10: 432-440.
25 Nasseri K, Strijers RLM, Dekhuijzen LS, Buster M, Bertelsmann FW: Reproducibility of different methods for diagnosing and monitoring diabetic neuropathy *Electromyogr Clin Neurophysiol.,* 1998[Medline]; 38: 295-299.
26 DCCT Research Group; The Diabetes Control and Complications Trial (DCCT) design and methodologic considerations for the feasibility phase *Diabetes.,* 1986[Abstract]; 35: 530-545.
27 Scott LV, Tesfaye S Measurement of somatic neuropathy for clinical practice and clinical trials. *Curr Diab Rep* Dec.,, 2001; 1(3): 208-215.
28 Koopman RJ, Mainous AG, Liszka HA et al Evidence of nephropathy and peripheral neuropathy in US adults with undiagnosed diabetes *Annuls of Family Medicine.,* 2006; 4: 427-432
29 Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AIM Multicenter study of the incidence of and predictive risk factors tor diabetic neuropathic foot ulceration. *Diabetes Care.,* 1998; 21: 107-l075.[Abstract]
30 Galer BS, Gianas A, Jensen MP Painful diabetic neuropathy: epidemiology, pain description, and quality of life *Diabetes Res Clin Pract.,* 2000; 47: 123-128[CrossRef][ISI][Medline]
31 Ad Hoc Panel on Endpoints for Diabetic Neuropathy Trials: Positive neuropathic sensory symptoms as endpoints in diabetic neuropathy trials. J *Neurol Sci.,* 2001 [Medline]; 189: 3-6
32 Tolle T, Xu X, Sadpsky AB Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns *Diabetes Complications.,* b2006; 20: 26-33.
33 Forsblom CM, Sane T, Groop PH *et al* Risk factors for mortality in type II (non-insulin-dependent) diabetes evidence of a role for neuropathy and a protective effect of HLA-DR4 *Diabetologia.,* 1998; 4: 1253-1262
34 Coppini DV, Bowtell PA, Weng C, et al Showing neuropathy is related to increased mortality in diabetic patients—a survival analysis using an accelerated failure time model *J Clin Epidemiol 2WQ*\ 53: 519-523[CrossRef[Medline]
35 Vinik E, Hayes R, Oglesby A, et al The development and validation of the Norfolk OOL-DN a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. *Diabetes Technol Ther.,* 2005; 7: 497-508 Abstract
36 Apfel SC, Asbury A, Bril V, et al Positive neuropathic sensory symptoms as endpoints in diabetic neuropathy trials. *J Neural Sci.,* 2001; 189: 3-5 Abstract
37 Toinlinson DR Role of aldose reductase inhibitors in the treatment of diabetic polyneuropathy In: Dyck PJ, Thomas PK (eds) *Diabetic Neuropathy* (2nd ed). Philadelphia, W B Saunders Company, 1999; 330-340.
38 Gregersen G: Myo-inositol supplementation In: Dyck PJ, Thomas PK, Asbury AK, Winegrad Al, Porte D (eds) *Diabetic Neuropathy (*1st ed) Philadelphia, W B Saunders Company, 1987; 188-189.
39 Cameron NE, Cotter MA Role of linolenic acid in diabetic polyneuropathy In Dyck PJ, Thomas PK (eds). *Diabetic Neuropath* (2nd ed) Philadelphia, W B Saunders Company, 1999; 359-367.
40 Jamal GA, Carmichael H: The effect of gamma-Iinolenic acid on human diabetic peripheral neuropathy a double-blind placebo-controlled trial *Diabet Med.,* 1990; 7: 319-3 2 3 [Medline]
41 Cameron NE, Cotter MA, Low PA: Nerve blood flow in early experimental diabetes in rats relation to conduction deficits. *Am J Physiol.,* 1991; 261 E1-E8 [Abstract/Free Full Text]
42 Yasuda H, Kikkawa R Role of antiprostaglandins in diabetic neuropathy In: Dyck PJ, Thomas PK (eds) *Diabetic Neuropathy* (2nd ed) Philadelphia, W B Saunders Company, 1999; 368-376
43 Feldman EL, Windebank AJ: Growth factors and peripheral neuropathy In. Dyck PJ, Thomas PK (eds) *Diabetic Neuropathy* (2nd ed). Philadelphia, \V B Saunders Company, 1999; 377-386.
44 Brownlee M: Advanced glycation end products and diabetic peripheral neuropath} In Dyck PJ, Thomas PK (eds) *Diabetic Neuropathy* (2nd ed). Philadelphia, WB Saunders Company, 1999; 353-

358.
45 Quatraro A, Roca P, Donzella C, Acampora R, Marfella R, Giugliano D Acetyl-L-carnittne for symptomatic diabetic neuropathy (Letter). *Diabetologia.*, 1995; 38: 123. [Medline]
46 Low PA, Nickander KK, Scionti L Role of hypoxia, oxidative stress, and excitatory neurotoxins in diabetic neuropathy In: *Dyck PJ, Thomas PK* (eds) *Diabetic Neuropathy* (2nd ed) Philadelplua, W B Saunders Company, 1999; 317-329.
47 Malik RA, Williamson S, Abbott C et al: Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy randomised double-blind controlled trial *Lancet.*, 1998; 352: 1978-198I.[Medline]
48 Low PA, Nickander KK: Oxygen free radical effects in sciatic nerve in experimental diabetes *Diabetes.*, 1991; 40: 873-877.[Abstract]
49 Morello C M, Leckband SG, Stoner CP et al. Randomized Double-blind Study Comparing the Efficacy of Gabapentin With Amitriptyline on Diabetic Peripheral Neuropathy Pain *Arch Intern Med.* 19Q9; 1 59 19.3 1-1937.
50 Cameron NE, Cotter MA, Maxfield EK: Anti-oxidant treatment prevents the development of peripheral nerve dysfunction in streptozotocin-diabetic rats., 36: 299-304£MedJine]
51 Nagamatsu M, Nickander KK, Schmelzer JD, Raya A, Wittrock DA, Tritscbler H, Low PA Lipoic acid improves nerve blood flow, reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy *Diabetes Care.*, 1995; 18: 1 160-H67F [Abstract]
52 Suzuki Y, Mizuno M, Tritschler HJ, Packer L Redox regulation of NF-kB DNA binding activity by dihydrolipoate *BBRC.*, 1995; 36: 241-246.
53 Strokov IA, Kozlova NA, Mozolevsky YV Efficacy of iv administered trometamol salt of thioctic (aipha-fipoic) acid in diabetic neuropathy *'Zh-Nevrol-Psikhiatr-Im-S-S-Korsakova.*, 1999; 99: 18-22.
54 Pfeifer MA, Ross DR^ Schrage JP et al A highly successful and novel model for treatment of Chronic painful diabetic peripheral neuropathy, *Diabetes care.*, 1993; 16: 1103.
55 The Capsaicin Study Group Treatment of painful diabetic neuropathy with topical capsaicin a multicentre, double-blind, vehicle-controlled *Arch lnt Meet.*, 1991; 151 2225.
56 Ezzo J, Donner T, Nickols D, Cox M Is Massage Useful in the Management of Diabetes? A Systematic Review. *Diabetes Spectrum.*, 2001; 14: 218-224.
57 Kishi M, Tanabe J, Schmelzer JD, Low PA Morphometry of dorsal root ganglion of chronic experimental diabetic neuropathy *Diabetes.*, 2002; 51: 819—824[Abstract/Free Full Text]
58 Toyokuni S Reactive oxygen species-induced molecular damage and its application in pathology *Pathol Int.*, 1999; 49: 91-102. [Medline]