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Painful diabetic peripheral neuropathy: A current concepts review of clinical examination findings for use in patient selection for treatment and research

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ABSTRACT

(a) Title: Painful diabetic peripheral neuropathy- a current concepts review of clinical examination findings for use in patient selection for treatment and research., (b) Abstract body: Diabetes is a global epidemic and one of the most leading complications of diabetes is peripheral neuropathy. Recent research and clinical practice focus is growing on symptomatic or painful diabetic peripheral neuropathy (PDPN) due to the rising healthcare costs and impending disability. The objective of this review is to elaborate the clinical examination findings in symptomatic PDPN patients. The various clinical examination methods reported in MEDLINE, EMBASE, SCOPUS, Ovid, CINAHL and Google Scholar were searched independently and 66 suitable trials were identified. The selected studies are grouped under each of the clinical examination findings and are described under chief complaints, presenting history, subjective examination, objective examination, investigations and differential diagnosis in the review. Through a thorough history and subjective examination, identification of possible mechanism of neuropathic pain in these patients would facilitate focused objective examination that can again be confirmed using investigations. A proposed clinical decision-making algorithm is presented after this review to base treatment decisions from clinical findings. The clinical examination findings explained in this review would facilitate clinicians, researchers and stakeholders to understand the complex clinical presentation of symptomatic patients with painful diabetic peripheral neuropathy, and to develop better assessment methods in the future for earlier identification of such patients to initiate further management.

Key words: symptoms and signs, diabetic neuropathy, neuropathic pain, assessment.

INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[1]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030[2]. The microvascular complications of diabetes are termed collectively as "triopathy" which includes retinopathy, neuropathy and nephropathy and the macrovascular complications include

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peripheral vascular disease, cerebrovascular disease and cardiovascular disease[3,4].

Diabetic peripheral neuropathy (DPN) is a common complication estimated to affect 30% to 50% of individuals with diabetes. Chronic sensorimotor distal symmetric polyneuropathy is the most common form of DPN. The prevalence of neuropathy in type 2 diabetes ranges from 27% to 63% and from 14% to 70% in diabetes mellitus in general.[4] The higher prevalence of neuropathy in type 2 diabetes patients is related to greater age, male gender, longer diabetes duration, higher levels of glycosylated hemoglobin, lower HDL cholesterol, smoking; peripheral vascular disease and insulin use[5].

Diabetic neuropathy has been defined as Peripheral somatic or autonomic nerve damage attributable solely to diabetes mellitus. It may be of two types- symmetrical and asymmetrical. The symmetrical type was the commonest and it affects the sensory and autonomic functions of mostly peripheral nerves whereas the asymmetrical type affects the cranial nerves in their sensory and motor functions.[6] The first description of "diabetic neuropathy as a presence of pain and paresthesiae in lower limbs" was done by Rollo in 1798.[7] The consensus of opinion at the San Antonio conference on diabetic neuropathy was that diabetic neuropathy was "a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical that occurs in a setting of diabetes mellitus without other causes of neuropathy. The neuropathic disorder includes manifestations in both somatic and/or autonomic parts of the nervous system."

Diabetic peripheral neuropathic pain (DPNP) affects approximately 11% of patients with diabetic peripheral neuropathy (DPN). The most common type of neuropathy in DM is DPN, with up to 50% of patients experiencing some degree of painful symptoms and 10% to 20% having symptoms severe enough to warrant treatment. A classic population- based study found some degree of neuropathy in 66% of patients with DM. Among those with type 1 and type 2 DM, 54% and 45%, respectively, had DPN and 15% and 13%, respectively, were symptomatic.[8]

The aim of this review is to elaborate the clinical examination findings in the patients with PDPN to facilitate an evidence-informed clinical decision-making for identification of suitable patient presentation prior to treatment administration or inclusion in research.

METHODS OF THE REVIEW

The various clinical examination methods reported in MEDLINE, EMBASE, SCOPUS, Ovid, CINAHL and Google Scholar were searched independently using key terms "symptoms" OR "signs" OR "clinical" OR "features" OR "findings" AND "diabetic" AND "neuropathy." Reviews, original articles and commentaries were considered accepted for our review. After the independent blinded search, the authors retrieved 122 potentially eligible articles and then they were screened with titles and abstract to obtain the final 66 suitable trials for this review. Consensus was obtained between the authors at various stages of the review process to organize the studies under the probable sub-headings of clinical examination findings. Of the 56 excluded studies, 33 were on treatments, 11 were on laboratory or experimental diabetic neuropathy models, 7 were not in English and 5 were case reports.

MAIN FINDINGS OF THE REVIEW

CHIEF PATIENT COMPLAINTS

Considering the findings of an earlier survey by American Diabetes Association (ADA),[9] patients with PDPN rarely know that they are having neuropathy, symptom identification may be delayed in these patients. Symptom reporting often occurs at a stage when the presentation gets chronic and disabling.[10] Functional issues get priority when activities get restricted or painfully limited,[11] with sleep disturbances,[12] thus affecting their daily living and quality of life itself.[13] Patients also report symptoms in a vague description

since they are not much aware of the temporal characteristics[14] (descriptors such as squeezing, cramping, lightning, throbbing etc) or understand their implications.

HISTORY OF PRESENTING COMPLAINT

The symptoms usually tend to get worsen at night or at rest, but manageable during activity or movements. There was also a strong association reported between symptom alterations with changes in environmental temperatures suggesting a vascular comorbidity in these patients.[15] Neuropathic symptoms or complaints arising due to peripheral nerve involvement are common such as pain, altered sensation, weakness and loss of related function such as gait.[16] Loss of proprioceptive sensation[17] in the lower extremities may lead to balance impairments and history of falls.[18] Loss of thermal and protective sensation may predispose tissue damage leading to foot ulcerations.[19] Longer duration or persistent symptoms lead to musculoskeletal manifestations like restricted joint mobility,[20] muscle flexibility and biomechanical alterations in soft tissues of the lower extremities. Limited ankle joint mobility[21] may in turn lead to altered neural tissue dynamics leading to neural tissue symptoms.[22] Neural tissue symptoms such as numbness, tingling, pins and needle sensation, shooting pain, pulling pain, ant-crawling sensations felt along the course of the nerve may implicate "nerve trunk pain" in these patients.[23] Other positive symptoms of hyperalgesia, hyperpathia and allodynia are also common. The characteristic features of "diabetic foot[24]-" foot trauma, ulceration, then infection, gangrene, and possibly amputation should never be missed by the assessing clinician.

ASSOCIATED COMPLAINTS

Neuropathy is one of three major microvascular complications of diabetes, named collectively together as the "triopathy[4]" for neuropathy, retinopathy[25,26] and nephropathy.[27] The assessing clinician should be aware that symptoms from other complications are not uncommon in these patients. Neuropathy itself might lead to other associated complications of diabetes in these patients.[28] The macrovascular complications are also three- peripheral vascular disease, cerebrovascular disease and cardiovascular disease.[4] It is hence not uncommon for patients to report symptoms of these disorders together, and even if not, it is the responsibility of the clinician to rule out the co-existing complications of diabetes mellitus or to ensure a stable medical condition prior to administration of further testing or treatment. Other rare, but not so uncommon are the features of sympathetic[29,30] and parasympathetic[30] nerve involvement in these patients. Symptoms from other comorbidities such as obesity[31-33], hypertension[33] and altered psychosocial states[34] should also be considered.

NEUROPATHIC PAIN

The International Association for the Study of Pain (IASP) defined neuropathic pain as, "pain caused or arising from the lesion or dysfunction of the nervous system."[35] The term "dysfunction" here encompasses anatomical and/or physiological abnormality. Central neuropathic pain arises from central nervous system dysfunction and peripheral neuropathic pain arises from peripheral nervous system dysfunctions. Peripheral nervous system dysfunction clinically manifest as peripheral neuropathies in a large proportion of patients, presenting either as painful or painless neuropathies.

PAINFUL VERSUS PAINLESS NEUROPATHY

Identification of the pain presentations and categorizing the DPN into painful or painless enhances therapeutic decision-making.[36] The two types are identified by their typical descriptors for neuropathic pain- painful

versus non-painful presentations-as descriptions of positive neuropathic sensory symptoms; Refer to table-1 for comparison of clinical findings between painful and painless diabetic peripheral neuropathies.

CLASSIFICATION OF DIABETIC NEUROPATHY (DN

There are seven major types of diabetic neuropathy- distal symmetric polyneuropathy, autonomic neuropathy, nerve entrapment syndromes,proximal asymmetric mononeuropathy (diabetic amyotrophy), truncal radiculopathy, cranial mononeuropathy, and chronic inflammatory demyelinating polyneuropathy.[44]

TYPES OF DIABETIC NEUROPATHY:[39,45] RAPIDLY REVERSIBLE

1. Hyperglycemic neuropathy

Generalised symmetrical polyneuropathies

2. Sensorimotor (chronic)

3. Acute sensory

4. Autonomic

Focal and multifocal neuropathies

5. Cranial

6. Thoracolumbar radiculoneuropathy

7. Focal limb

8. Proximal motor (amyotrophy)

Superimposed chronic inflammatory demyelinating neuropathy

CHRONIC SENSORIMOTOR

Gradual, insidious

Burning pain, paresthesiae, numbness, weight loss unusual.

0 to ++

Stocking and glove sensory loss; absent ankle reflexes

Increased prevalence

Abnormalities unusual in motor and sensory nerves

Symptoms may persist intermittently for years; at risk of foot ulceration

STAGES OF NEUROPATHY- DPN:[39,46,47]

Four stages have been reported. No neuropathy (no symptoms or signs), clinical neuropathy (chronic and acute painful), painless with complete/partial sensory loss (numbness/ deadness of feet or no symptoms, painless injury, reduced/ absent sensation, reduced thermal sensitivity, absent reflexes); and late complications (foot lesions, neuropathic deformity, nontraumatic amputation). Clinical neuropathy is further subdivided into chronic painful (burning, shooting, stabbing pains with or without "pins and needles" increased at night; absent sensation to several modalities; reduced / absent reflexes) and acute painful (severe symptoms as chronic- hyperesthesiae common; may follow initiation of insulin in poorly controlled diabetes, signs minor or absent) neuropathy.

STAGING SEVERITY OF DIABETIC POLYNEUROPATHY:[39,47]

N0- No objective evidence of DN

N1- Asymptomatic polyneuropathy; N1a- No symptoms or signs but neuropathic test abnormalities, N1b- Test abnormalities plus neuropathy impairment of neurological exam.

N2- Symptomatic neuropathy; N2a- Symptoms, signs and test abnormality, N2B- N2a plus significant ankle dorsiflexor weakness, N3- Disabling polyneuropathy.

SMALL VS LARGE FIBER DIABETIC PERIPHERAL NEUROPATHY:[36,48,49]

Small fiber neuropathy- pain predominates (c-fiber type), often burning and superficial; allodynia (pain from normal stimuli such as

bed sheets); hypoalgesia in late stages; defective warm thermal sensation; defective autonomic function; decreased sweating (dry feet); and impaired vasodilatation (cold hands/ feet); intact reflexes and motor strength; electrophysiologically silent; loss of cutaneous nerve fibers using PGP 9.5 staining; diagnosed by clinical quantitative sensory testing abnormalities of touch, temperature and autonomic function tests and risk for foot ulceration and subsequent gangrene.

Large fiber neuropathy- may involve sensory or motor nerves; most distal nerves affected first ("stocking-glove" pattern); more neurologic signs than symptoms; impaired vibratory perception; depressed or absent deep tendon reflexes; and pain is deep-described as gnawing like a toothache or even cramping (Aä- pain) sensory ataxia; small muscle wasting; Achilles tendon shortening with pes equinus; and increased blood flow (hot foot).

ELECTROPHYSIOLOGIC STUDIES

Considered to be as the gold standard among the evaluation tools in patients with peripheral neuropathies in general and diabetic neuropathies of late, electrophysiologic studies[50] comprising of electromyography and nerve conduction studies[51] form a special tool for the clinician. Peripheral nerve conduction is impaired in diabetic neuropathy[52] that can often be detected in early stages of the disorder using lower extremity peripheral nerve conduction studies.[53] These tests may comprise of nerve conduction velocities, latency, F-wave studies, and nerve action potentials.

QUANTITATIVE SENSORY TESTING

Laboratory assessment[54] of patients with PDPN includes objective quantification of sensation assessed in terms of large and small fiber function termed as quantitative sensory testing.[55] Touch sensation is quantified with Semmes-Weinstein monofilaments or Von Frey hairs where insensitivity to 5-gm monofilament was highly suggestive of neuropathy in these patients.[54] Two-point discrimination was assessed using Dellon's two-point discriminator.[54] Vibration perception thresholds (VPT) are to be assessed using Biothesiometry equipments like Vibramater[54,55,56] and thermal perception threshold testing using Medoc instruments. A vibration threshold of greater than 25V on biothesiometer indicates presence of neuropathy and this screening method was widely used in clinical practice and research.[57] Thermal perception thresholds[59] comprise testing of heat perception threshold (HPT) and cooling perception thresholds (CPT).[60,61] One of the recent quantitative sensory test measures evolved and studied in these patients is the current perception threshold testing.[62]

Le Quesne et al[63] explained a clinical classification of diabetic peripheral neuropathy into three groups based upon quantitative sensory testing abnormalities in VPT (Aâ fibers- large diameter, myelinated), CPT (Aä fibers- large diameter, unmyelinated), HPT (C fibers- small diameter, unmyelinated);

Group1- patients with long standing diabetes but clinically insignificant neuropathy, patients attending a diabetic clinic for more than 20 years who had not complained of symptoms attributable to peripheral neuropathy.

Group 2- patients with mild neuropathy, patients, who were taking part in a drug trial, who had clinical evidence of mild neuropathy on the basis of abnormal vibration perception assessed in the outpatient clinic but with no foot lesions.

Group 3- patients with neuropathic foot lesions, patients with neuropathy and

various foot complications of diabetes such as interdigital sepsis and paronychia, neuropathic plantar ulcers, Charcot arthropathy of the feet.

NEURODYNAMIC TESTING

Neurodynamics is the concept based on a close interaction of mechanics and physiology

of the nervous system which is to be considered while assessing and treating patients via nervous system mobilization and manual therapy.[64] This assessment and treatment approach allows us to physically test the dynamics and the associated sensitivity of the nervous system.[65] Neural mechanosensitivity as a presenting clinical feature in many of the lower extremity musculoskeletal symptoms[66] was reported in the literature for plantar heel pain,[67] lumbar radiculopathy,[68] hamstring strain,[69] ankle sprain[70,71] and tarsal tunnel syndrome.[72]

The physical signs of neural tissue involvement include adverse responses to neural tissue provocative testing and mechanical allodynia in response to palpation of nerve trunks.[73] A combination of multiple joint movements performed to mechanically test the peripheral nerve is termed as neurodynamic testing.[74] There are four upper limb neurodynamic tests, seven lower limb neurodynamic tests and two spinal neurodynamic tests. The relationship between neuromechanics and neurophysiology was proposed by Butler[75] and Shacklock,[76] and studied recently by many authors where upper limb neurodynamic mobilization influenced the thermal perception thresholds[77] and current perception thresholds.[78] Lower extremity neurodynamic test like straight leg raising (SLR) test was used for years to aid in the diagnosis of lumbar disc lesions and nerve root compression since its initial documented description by J. J. Frost in 1881.[79] SLR mobilization was studied as a treatment technique in spinal surgery patients by authors earlier.[80,81]

Neurophysiological effects of SLR test was studied by Ridehalgh et al[82] who examined the effects of superficial peroneal nerve tensioner technique- a modified straight leg raise with plantar flexion and inversion on vibration perception thresholds (VPT) and the findings showed that the tensioner technique increased the VPT compared to sham technique but the effects were reversible within ten minutes among both runners and non-runners. Earlier study by Humphreys et al[83] on ten healthy subjects, demonstrated longer tibial nerve F-wave latencies when measured in straight leg raise position, proposedly indicating the neurophysiological effect of the SLR position and the author recommended neurophysiologic testing in nerve lengthened positions so as to elicit subtle neural involvement signs.

Earlier study by Coppieters and Butler[84] suggested that the nerve slider and tensioner techniques prove to be a valuable treatment tool in patients with neuropathies. Coppieters et al[85] also stressed the importance and safety of use of slider techniques in increasing nerve mobility and excursion without compromising neural circulation when in-vivo ultrasound imaging for median nerve was used to compare the slider and tensioner techniques. Considering the growing evidence in favor of neurodynamic mobilization for patients with neural dysfunctions[86] and for patients with peripheral neuropathic pain,[87] knowledge of normal responses not only explain underlying mechanisms but also tend to establish a clinical and research baseline on which clinical decision making could be further implemented in patient populations with lower extremity neuropathic symptoms. Recent paradigm shift towards evidence-informed clinical decision making in physical therapy[88] warrants clinicians and researchers to further explore this area.

Currently there are many research works in progress in this area, to contribute to the already expanding body of evidence witnessed by growing number of randomized clinical trials indexed in physiotherapy evidence database[89] and physical therapy treatment methods[90] for these patients on the effects of intervention using neurodynamic mobilization (nerve slider techniques and nerve massage) in patients with painful diabetic peripheral neuropathy[91-94] using validated clinical assessment scales[95] to score the severity, impairment of function and impact on quality of life in these patients.

We present our proposed model of patient selection and treatment decision-making here below in table-2.

CONCLUSION

We presented a detailed review of clinical features and clinical examination findings of patients with painful diabetic peripheral neuropathies to facilitate and encourage future research to develop better treatment methods in this area. The proposed model of clinical decision-making is yet to be validated using well-designed clinical trials[97,98] and using advanced lab investigations such as real time ultrasonography for assessing longitudinal nerve motion[99] and then tested further to

Table 1: Comparison of clinical findings between painful and painless diabetic peripheral neuropathies

Description	Painful	Non-painful
Nature of symptoms[37-39]	Prickling, tingling, knife-like, electric shock-like, squeezing, constricting, hurting, burning, freezing, throbbing, allodynia, hyperalgesia.	"Dead," thick, stiff, asleep, prickling, numbness, tingling.
Neuropathy disability score[40]	Higher	Lower
CPT (current perception thresholds)[40]	Similar	Similar
VPT (vibration perception thresholds)[40]	Similar	Similar
Electrophysiologic testing (peroneal nerve motor conduction velocity)[40]	Similar	Similar
Autonomic nervous system function tests[40]	Similar	Similar
Interleukin IL-2 mRNA[41]	Two-fold higher	Lower
Tumor Necrosis Factor-TNF mRNA[41]	Two-fold higher	Lower
Protein levels[41]	Two-fold higher	Lower
Small-fiber dysfunction – cooling & warming thresholds[42]	Uniform dysfunction	Uniformly severe dysfunction
Large-fiber dysfunction-nerve conduction studies & vibration perception thresholds[42]	Wide range abnormal.	Uniformly severe dysfunction (peroneal motor nerve conduction velocity)
Sympathetic dysfunction-postural drop in blood pressure & plasma noradrenaline levels[42]	Maintained normal.	Uniformly severe dysfunction
Parasympathetic dysfunction-heart-rate dependent cardiac autonomic reflexes[42]	Abnormal	Uniformly severe dysfunction
Abnormal blood flow[43]	Reduced peripheral vascular resistance	Severely reduced peripheral vascular resistance leads to recurrent foot ulceration

Table 2: A proposed evidence-informed clinical decision-making algorithm for management of patients with painful diabetic peripheral neuropathy

Patient presentation	Proposed probable choice of management
Constant symptoms	
Comorbid anxiety and depression	Tricyclic antidepressant drugs[96]
Sleep disturbances	Anti-convulsant drugs and opioid medications[96]
Constant unrelenting symptoms	Serotonin norepinephrine reuptake inhibitor drugs[96]
With neurological deficits or negative symptoms, with abnormal nerve conduction studies and quantitative sensory tests	Vitamin B-12 and anti-epileptic drugs[96]
Aggravated at rest	Transcutaneous electrical nerve stimulation (TENS), monochromatic near-infra-red energy (MIRE) therapy as an adjunct[90] to pharmacotherapy[96]
Intermittent symptoms	
Aggravated with particular positions or touch	Topical local anesthetic application[96]
Aggravated with touch or other cutaneous thermal stimuli	Topical capsaicin[96]
Aggravated with movements	Neurodynamic testing and mobilization[91-94]

develop clinical prediction rules[100] and clinical practice guidelines in the future.

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REFERENCES

1. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications - Part 1: Diagnosis and Classification of Diabetes Mellitus. Report of a WHO Consultation. Geneva, 1999.
2. Wild S, Roglic G, Green J, Sicree R, King H. Global prevalence of diabetes- estimates for the year 2000 and projections for 2030. Diabetes Care, 2004; 27: 1047-1053.
3. Bell DSH. Current status of diabetes treatment. Southern Medical Journal, 2002; 95: 24-29.
4. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Physical Therapy, 2008; 88: 1254-1264.
5. Wheeler S, Singh N, Boyko EJ. The epidemiology of diabetic neuropathy. In. Veves A, Malik R. Eds. Diabetic Neuropathy: Clinical Management. Second edition, Springer, 2007.
6. Horowitz SH. Diabetic neuropathy. Clinical Orthopaedics and Related Research, 1993; 296: 78-85.
7. Fernando D. Diabetic neuropathy: clinical features and natural history. International Journal of Diabetes in Developing Countries, 1995; 15:55-60.
8. Argoff CE, Cole BE, Fishbain DA, Irving GA. Diabetic peripheral neuropathic pain- clinical and quality of life issues. Mayo Clinic Proceedings, 2006; 81(4, suppl): s3-s11.
9. Diabetes Information Library. American Diabetes Association survey finds most people with diabetes don't know about highly prevalent, serious complications. http://www.diabeteslibrary.org/PrintArticle.aspx?ArticleID=675. Accessed January 5, 2010.

10. Hoffman DL, Sadosky A, Alvir J. Cross-national burden of painful diabetic peripheral neuropathy in Asia, Latin America and the Middle East. Pain Pract, 2009; 9: 35-42.
11. Gore M, Brandenburg NA, Hoffman DL, Tai KS, Stacey B. Burden of illness in painful diabetic peripheral neuropathy: the patient's perspectives. J Pain, 2006; 7: 892-900.
12. Zelman DC, Brandenburg NA, Gore M. Sleep impairment in patients with painful diabetic peripheral neuropathy. Clin J Pain, 2006; 22: 681-685.
13. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity and impact of painful diabetic peripheral neuropathy in type-2 diabetes. Diabetes Care, 2006; 29: 1518-1522.
14. Jensen MP, Friedman M, Bonzo D, Richards P. The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. Clin J Pain, 2006; 22: 97-103.
15. Benbow SJ, Chan AW, Bowsher D, Mafarlane IA, Williams G. A prospective study of painful symptoms, small-fibre function and peripheral vascular disease in chronic painful diabetic neuropathy. Diabet Med, 1994; 11: 17-21.
16. Salsich GB, Brown M, Mueller MJ. Relationships between plantar flexor muscle stiffness, strength and range of motion in subjects with diabetes-peripheral neuropathy compared to age-matched controls. Journal of Orthopaedic and Sports Physical Therapy, 2000; 30(8): 473-483.
17. Van Deursen RWM, Simoneau GG. Foot and ankle sensory neuropathy, proprioception and postural stability. Journal of Orthopaedic and Sports Physical Therapy, 1999; 29(12): 718-726.
18. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care,* 2004a; 27: 1458-1486.
19. Mueller MJ, Diamond JE. Biomechanical Treatment Approach to Diabetic Plantar Ulcers-A Case Report. Physical Therapy, 1988; 68: 1917-1920.
20. Starkman HS, Gleason RE, Rand LI, Miller DE, Soeldner JS. Limited joint mobility (LJM) of the hand in patients with diabetes mellitus: relation to chronic complications. Annals of the Rheumatic Diseases, 1986; 45: 130-135.
21. Mueller MJ, Diamond JE, Delitto A, Sinacore DR. Insensitivity, limited joint mobility and plantar ulcers in patients with diabetes mellitus. Physical Therapy, 1989; 69(6): 453-462.
22. Hajrasouliha AR, Tavakoli S, Esteki A, Nafisi S, Noorolahi- Moghaddam H. Abnormal viscoelastic behaviour of passive ankle joint movement in diabetic patients: an early or a late complication? Diabetologia, 2005; 48: 1225-1228.
23. Hall TM, Elvey RL. Nerve trunk pain: physical diagnosis and treatment. Man Ther, 1999; 4: 63-73.
24. Gavin LA, Stess RM, Goldstone J. Prevention and treatment of foot problems in diabetes mellitus- a comprehensive program. Western Journal of Medicine, 1993; 158: 47-55.
25. Root HF, Pote WH Jr, Frehner H. Triopathy of diabetes: sequence of neuropathy, retinopathy and nephropathy in 155 patients. Archives of Internal Medicine, 1954; 94(6): 931-941.
26. Porta M, Bandello F. Diabetic retinopathy- a clinical update. Diabetologia, 2002; 45: 1617-1634.
27. Rossing P. Prediction, progression and prevention of diabetic nephropathy- the Mikowski lecture 2005. Diabetologia, 2006; 49: 11-19.
28. Chan L, Terashima T, Fujimiya M, Kojima H. Chronic diabetic complications: the body's adaptive response to hyperglycemia gone awry? Transactions of the American Clinical and Climatological Association, 2006; 117: 341-352.
29. Watkins PJ, Edmonds ME. Sympathetic nerve failure in diabetes. Diabetologia, 1983; 25: 73-77.
30. Freccero C, Svensson H, Bornmyr S, Wollmer P, Sundevist G. Sympathetic and parasympathetic neuropathy are frequent in both type-1 and type-2 diabetic patients. Diabetes Care, 2004; 27(12): 2936-2941.
31. Porte Jr. D, Seeley RJ, Woods SC, Baskin DG, Figlewicz DP, Schwartz MW. Obesity, diabetes and the central nervous system. Diabetologia, 1998; 41: 863-881.
32. Hilton TN, Tuttle LJ, Bohnert KL, et al. Excessive adipose tissue infiltration in skeletal muscle in individuals with obesity, diabetes mellitus, and peripheral neuropathy: association with performance and function. *Phys Ther,* 2008; 88: 1336-1344.
33. Kirkness CS, Marcus RL, LaStayo PC, et al. Diabetes and associated risk factors in patients referred for physical therapy in a national primary care electronic medical record database. Physical Therapy, 2008; 88(11): 1408-1416.

34. Vileikyte L, Leventhal H, Gonzalez JS, Peyrot M, Rubin RR, Ulbecht JS et al. Diabetic peripheral neuropathy and depressive symptoms- the association revisited. Diabetes Care, 2005; 28(10): 2378-2383.

35. Merskey H, Bogduk N. Classification of chronic pain. Seattle: International association for the study of pain (IASP) Press, 1994.

.36. Tanenberg RJ. Diabetic peripheral neuropathy: painful or painless. Hospital Physician 2009; 45(7): 1-8.

37. Apfel SC, Asbury AK, Bril V, Burns TM, Campbell JN, Chalk CH et al. Positive neuropathic sensory symptoms as endpoints in diabetic neuropathy trials. Journal of Neurologic Sciences, 2001; 189: 3-5.

38. Boulton AJM. Management of diabetic peripheral neuropathy. *Clin Diabetes,* 2005b; 23: 9-15.

39. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care,* 2004a; 27: 1458-1486.

40. Veves A, Young MJ, Manes C, Boulton AJ. Differences in peripheral and autonomic nerve function measurements in painful and painless neuropathy: a clinical study. Diabetes Care, 1994; 17(1): 1200-1202.

41. Uceyler N, Rogausch JP, Toyka KV, Sommer C. Differential expression of cytolines in painful and painless neuropathies. Neurology, 2007; 69: 42-49.

42. Tsigos C, White A, Young RJ. Discrimination between painful and painless diabetic neuropathy based on testing of large somatic nerve and sympathetic nerve function. Diabetic Medicine, 2009; 9(4): 359-365.

43. Corbin DOC, Young RJ, Morrison DC, Hoskins P, McDicken WN, Housley E et al. Blood flow in the foot, polyneuropathy and foot ulceration in diabetes mellitus. Diabetologia, 1987; 30: 468-473.

44. Wheeler S, Singh N, Boyko EJ. The epidemiology of diabetic neuropathy. In. Veves A, Malik R. Eds. Diabetic Neuropathy: Clinical Management. Second edition, Springer, 2007.

45. Thomas PK. Classification, differential diagnosis and staging of diabetic peripheral neuropathy. Diabetes, (Suppl 2) 1997; 46: S54-S57.

46. Dyck PJ. Severity and staging of diabetic polyneuropathy. In Textbook of Diabetic Neuropathy. Gries FA, Cameron NE, Low PA, Ziegler D, Eds. Stuttgart, Thieme, 2003; 170-175.

47. Dyck PJ, Dyck PJB. Diabetic polyneuropathy: section III. In Diabetic Neuropathy. 2nd ed. Dyck PJ, Thomas PK, Eds. Philadelphia, W.B. Saunders, 1999; 255-278.

48. Vinik AI, Park TS, Stansbery KB, Pittenger GL. Diabetic neuropathies. Diabetologia, 2000; 43: 957-973.

49. Vinik AI, Mehrabyan A. Diabetic neuropathies. Medical Clinics of North America, 2004b; 88: 947-999.

50. Laontagne A, Buchtal F. Electrophysiological studies in diabetic neuropathy. J Neurol Neurosurg Psychiat, 1970; 33: 442-452.

51. Gilliatt RW, Willison RG. Peripheral nerve conduction in diabetic neuropathy. J Neurol Neurosurg Psychiat, 1962; 25: 11-18.

52. Walker FO, Chaudhry V, Corse A, Freimer ML, Glass JD, Mellits DE et al. Nerve conduction studies in diabetic neuropathy. Neurology, 1995; 45: 849-850.

53. Herrera E, Camargo DM, Delgado DC, Salvini TF. Reliability of superficial peroneal, sural, and medial plantar nerve conduction studies-analysis of statistical methods. J Clin Neurophysiol, 2009; 26: 372-379.

54. Das AK. Laboratory assessment of diabetic peripheral neuropathy. Int J Diab Dev Ctries, 1988; 6: 49-54.

55. Chong PST, Cros DP. American Association of Electrodiagnostic Medicine (AAEM) Practice Topic in Electrodiagnostic Medicine: Technology literature review: quantitative sensory testing. Muscle Nerve, 2004; 29: 734-747.

56. Duke J, McEvoy M, Sibbritt D, Guest M. Vibrotactile threshold measurement for detecting peripheral neuropathy: defining variability and a normal range for clinical and research use. Diabetologia, 2007; 50: 2305-2312.

57. Van Deursen RWM, Sanchez MM, Derr JA, Becker MB, Ulbrecht JS et al. Vibration perception threshold testing in patients with diabetic neuropathy : ceiling effects and reliability. Diabetic Medicine, 2001; 18: 469-475.

58. Guy RJC, Clark CA, Malcolm PN, Watkins PJ. Evaluation of thermal and vibration sensation in diabetic neuropathy. Diabetologia, 1985; 28: 131-137.

59. Viswanathan V, Snehalatha C, Seena R, Ramachandran A. Early recognition of diabetic

neuropathy: evaluation of a simple outpatient procedure using thermal perception. Postgrad Med J, 2002; 78: 541-542.

60. Dyck PJ, Bushek W, Spring EM, Karnes JL, Litchy WJ, O'Brien PC et al. Vibratory and cooling detection thresholds compared with other tests in diagnosing and staging diabetic neuropathy. Diabetes Care, 1987; 10: 432-440.
61. 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.
62. Masson EA, Veves A, Fernando D, Boulton AJM. Current perception thresholds: a new, quick and reproducible method for the assessment of peripheral neuropathy in diabetes mellitus. Diabetologia, 1989; 32: 724-728.
63. Le Quesne PM, Fowler CJ, Parkhouse N. Peripheral neuropathy profile in various groups of diabetics. Journal of Neurology, Neurosurgery and Psychiatry, 1990; 53: 558-563.
64. Shacklock MO. Neurodynamics. Physiotherapy, 1995; 81(1): 9-16.
65. Schroder JA. Manual therapy and neural mobilization- our approach and personal observations. Orthopaedic Practice, 2005; 16(4): 23-27.
66. George SZ. Characteristics of Patients With Lower Extremity Symptoms Treated With Slump Stretching: A Case Series. Journal of Orthopaedics and Sports Physical Therapy, 2002; 32(8): 391-398.
67. Alshami AM, Souvlis T, Coppieters MW. A review of plantar heel pain of neural origin: Differential diagnosis and management. Manual Therapy, 2008a; 13: 103-111.
68. Rabin A, Gerszten PC, Karausky P, Bunker CH, Potter DM, Welch WC. The sensitivity of the seated straight-leg raise test compared with the supine straight-leg raise test in patients presenting with magnetic resonance imaging evidence of lumbar nerve root compression. Archives of Physical Medicine and Rehabilitation, 2007; 88: 840-843.
69. Turl SE, George KP. Adverse neural tension: a factor in repetitive hamstring strain. Journal of Orthopaedics and Sports Physical Therapy, 1998; 27(1): 16-21.
70. Pabor S, Toppenberg R. An investigation of neural tissue involvement in ankle inversion sprains. Manual Therapy, 1996; 1(4): 192-197.
71. O'Neill PJ, Parks BG, Walsh R, Simmons LM, Miller SD. Excursion and strain of superficial peroneal nerve during inversion ankle sprain. The Journal of Bone and Joint Surgery (American), 2007; 89(A): 979-86
72. Alshami AM, Babri AS, Souvlis T, Coppieters MW. Biomechanical evaluation of two clinical tests for plantar heel pain: the dorsiflexion-eversion test for tarsal tunnel syndrome and the Windlass test for plantar fasciitis. Foot & Ankle International, 2007; 28(4): 499–505.
73. Hall TM, Elvey RL. Nerve trunk pain: physical diagnosis and treatment. Manual Therapy, 1999; 4(2): 63-73.
74. Shacklock MO. Clinical neurodynamics: a new system of musculoskeletal treatment. Edinburgh, New York: Elsevier Butterworth-Heinemann, 2005a.
75. Butler DS. Mobilisation of the nervous system. Melbourne: Churchill Livingstone, 1991.
76. Shacklock MO. Improving application of neurodynamic (neural tension) testing and treatments: A message to researchers and clinicians- Editorial. Manual Therapy, 2005b; 10: 175-179.
77. Beneciuk JM., Bishop MD, George SZ. Effects of Upper Extremity Neural Mobilization on Thermal Pain Sensitivity: A Sham-Controlled Study in Asymptomatic Participants. Journal of Orthopaedics and Sports Physical Therapy, 2009; 39(6): 428-438.
78. Constantini M, Tunks K, Wyatt C, Zettel H, MacDermid JC. Age and upper limb tension testing affects current perception thresholds. Journal of Hand Therapy, 2006; 19(3): 307-317.
79. Urban LM. The Straight-Leg-Raising Test: A Review. Journal of Orthopaedics and Sports Physical Therapy, 1981; 2(3): 117-133.
80. Kitteringham C. The effect of straight leg raise exercises after lumbar decompressive surgery- a pilot study. Physiotherapy 1996; 82(2): 115-123.
81. Scrimshaw S V, Maher C G. Randomized Controlled Trial of Neural Mobilization After Spinal Surgery. Spine, 2001; 26: 2647-2652.
82. Ridehalgh C, Greening J, Petty NJ. Effect of straight leg raise examination and treatment on vibration thresholds in the lower limb: a pilot study in asymptomatic subjects. Manual Therapy, 2005; 10(4): 136-143.
83. Humphreys CR, Coolry JL, Hoxie S, Davies SR. Effects of S1 nerve root lengthening on tibial

nerve F-wave latency in healthy subjects. Journal of Manipulative and Physiological Therapeutics, 1998; 21(2): 94–6.

84. Coppieters MW, Butler DS. Do 'sliders' slide and 'tensioners' tension? An analysis of neurodynamic techniques and considerations regarding their application. Manual Therapy, 2008; 13(3): 213–221.
85. Coppieters MW, Hough AD, Dilley A. Different nerve-gliding exercises induce different magnitudes of median nerve longitudinal excursion: an in-vivo study using dynamic ultrasound imaging. Journal of Orthopaedics and Sports Physical Therapy, 2009; 39(3): 164-171.
86. Ellis RF, Hing WA. Neural Mobilization: A Systematic Review of Randomized Controlled Trials with an Analysis of Therapeutic Efficacy. Journal of Manual and Manipulative Therapy, 2008; 16(1): 8-22.
87. Nee RJ, Butler D. Management of peripheral neuropathic pain: Integrating neurobiology, neurodynamics and clinical evidence. Physical Therapy in Sport, 2006; 7(4): 36-49.
88. Huijbregts PA. Orthopaedic manual physical therapy- history, development and future opportunities. Journal of Physical Therapy, 2010; 1: 11-24.
89. Kumar SP. Physical therapy- past, present and future. Journal of Physical Therapy, 2010; 1: 58-67.
90. Kumar SP, Adhikari P, Jeganathan PS, D'Souza SC. Physiotherapy Management of Painful Diabetic Peripheral Neuropathy: A Critical Review of Treatment Methods for Clinical Decision Making in Practice and Research. International Journal of Current Research and Review 2010; Under review.
91. Kumar SP, Adhikari PMR, Prabhu MM. Efficacy of Tibial nerve neurodynamic mobilization for neuropathic pain in type-II Diabetes mellitus- A Randomized Controlled Trial. *Indian Journal of Physiotherapy and Occupational Therapy,* 2010; In Press.
92. Kumar SP, Adhikari P, Jeganathan PS, Prabhu MM. A randomized sham-controlled study of efficacy of sciatic neurodynamic mobilization in painful diabetic peripheral neuropathy. *J Manual Manipulative Ther* 2010; Under review.
93. Kumar SP, Adhikari P, Jeganathan PS, Kumar V. Effects of tibial nerve longitudinal versus transverse massage on vibration and temperature thresholds in asymptomatic subjects. *Physiotherapy and Occupational Therapy Journal* 2010; Under review.
94. Kumar SP, Adhikari P, Jeganathan PS, Kumar V. Management of neuropathic pain- an evidence-based systematic review with a neurodynamic perspective. *Journal of Indian Association of Physiotherapists* 2010; Under review.
95. Kumar SP, Adhikari P, D'Souza SC, Jeganathan PS. Painful diabetic peripheral neuropathy: a current concepts review of clinical assessment scales for use in research and practice. *Int J Curr Res Rev,* 2010; 2(5): 3-13.
96. Kumar SP, Adhikari P, Jeganathan PS, D'Souza SC. Pharmacotherapy for painful diabetic peripheral neuropathy: a current concepts review of 15 systematic reviews and 103 controlled clinical trials in MEDLINE from 1954-2010. *Int J Curr Res Rev*. 2010; Under review.
97. Pfeifer MA, Schumer MP. Clinical trials of diabetic neuropathy: past, present and future. Diabetes, 1995; 44: 1355-1361.
98. Luft D. Interpretation of clinical trials for the treatment of diabetic neuropathy. Drugs Today, 1998; 34: 157.
99. Hough AD, Moore AP, Jones MP. Measuring longitudinal nerve motion using ultrasonography. Man Ther, 2000; 5: 173-180.
100. Beneciuk JM, Bishop MD, George SZ. Clinical prediction rules for physical therapy interventions: a systematic review. Phys Ther, 2009; 89: 114-124.