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Relationship between neuropathic pain, neurodynamics, sensory perception thresholds and quality of life in patients with painful diabetic peripheral neuropathy- a cross-sectional study., (UTRN 052343809-080920102668203)

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ABSTRACT

Background and purpose: Neuropathic pain (NP) is the most disabling complaint in patients with painful diabetic peripheral neuropathy (PDPN). Neurodynamics (ND) is assessment and treatment of neural tissue mechanosensitivity (NTM). Vibration perception threshold (VPT) is a measure of large fiber function and thermal perception threshold (TPT) is a measure of small fiber function. Quality of life (QoL) is a subjective perception of well-being in a person's living. The purpose of this study was to assess the inter-relationship between NP, NTM, VPT, TPT and QoL in patients with PDPN., **Materials and methods:** Assessor-blinded cross-sectional study with random-order test method was carried out on 112 PDPN patients of either gender (67 female, 45 male) of age … years with medically diagnosed distal symmetric polyneuropathy for at-least 3 years due to type-2 diabetes for greater than 5 years duration. The NP was assessed using neuropathic pain questionnaire (NPQ); ND assessment comprised of neurodynamic testing (range of motion in degrees) and nerve trunk palpation (presence of mechanical allodynia by clinical scoring) of sciatic, tibial and common peroneal nerves; VPT and TPT (which includes heat perception threshold- HPT and cold perception threshold- CPT) was assessed using biothesiometer; and QoL was measured using neuropathy-specific quality of life (NeuroQoL) instrument. The assessments were done only once per patient. Total assessment duration for each patient was one hour., **Data analysis and results:** All correlations were analyzed using Karl-Pearson's correlation co-efficient at 95% confidence interval using SPSS 11.5 for Windows., **Conclusion:** There was a statistically significant positive correlation found between neuropathic pain, neurodynamic testing, neuropathy-specific quality of life in patients with PDPN.

Key words: Diabetic neuropathy, clinical examination correlates, quantitative sensory testing, self-administered questionnaires, manual therapy examination

INTRODUCTION

Neuropathic pain was defined by International Association for the Study of Pain as "pain caused or arising from the lesion or dysfunction of the nervous system.[1]" Overall point prevalence estimates for neuropathic pain in general population was shown to be 8.2%.[2] Translating this prevalence to our Indian population of 10.28 billion[3,4] (according to 2001 census of Govt of India), it comes to .84 billion or 84 million people with neuropathic pain. Seven conditions were profoundly associated with disabling neuropathic pain, of which four were peripheral (chemotherapy-induced neuropathy, postsurgical neuropathic pain associated with breast and amputation surgery, post-herpetic neuralgia, and painful diabetic neuropathy) and three were central (post-stroke pain, spinal cord injury pain,

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multiple sclerosis pain).[5] The presence and severity of neuropathic pain was associated with a greater impairment in health-related quality of life of these patients.[6] The intense pain, other troublesome symptoms, limited efficacy and tolerability of available treatments, together with the impaired health and reduced work status, amount to a substantial burden for patients with peripheral neuropathic pain (PNP).[7]

Diabetic neuropathy is 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.[8] Diabetic peripheral neuropathy is one of the leading peripheral nervous system diseases leading to PNP. Peripheral nervous system dysfunction clinically manifest as peripheral neuropathies in a large proportion of diabetic patients, presenting either as painful or painless neuropathies.[9] Peripheral neuropathic pain often presents as a combination of nerve trunk pain and dysesthetic pain.[10] Nerve trunk pain is typically described as a deep and aching sensation that has been attributed to increased activity from mechanically or chemically sensitized nociceptors in the connective tissue sheaths of the nervous system (i.e. nervi nervorum and sinuvertebral nerves).[11] Dysesthetic pain is often characterized as an unfamiliar or abnormal sensation such as burning, tingling, electric, searing, drawing, or crawling,[8] and it is thought to be the result of volleys of impulses originating from damaged or regenerating afferent fibers that have become hyperexcitable (i.e. abnormal impulse generating sites).[12]

Nerve trunk pain typically presents as pain or abnormal sensations along the course of the peripheral nerve that can be clinically tested using the concept of neurodynamics. 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.[13] The foundation of knowledge behind neural tissue mechanosensitivity arose from the fact that peripheral nerve trunks in diabetic neuropathy exhibited mechanical allodynia[14] and mechanical hyperalgesia in animal and human experimental models of neuropathic pain.[15-18]

Neurodynamic assessment involves neurodynamic testing[19] and nerve palpation.[20] Neural tissue mechanosensitivity was to be confirmed during neurodynamic testing by positive response to structural differentiation so as to identify neural from the non-neural sources of patient symptoms.[13] Presence of mechanical allodynia on nerve trunk palpation was another key diagnostic sign of neural tissue mechanosensitivity.[11,21]

There are a numerous clinical assessment tools to evaluate neuropathic pain in painful diabetic peripheral neuropathy (PDPN) patients.[22] Of these, the neuropathic pain scale developed by Galer and Jensen,[23] and neuropathic pain questionnaire developed by Krause and Backonja[24] were well validated for their use in diabetic neuropathic pain clinical trials.[25]

Of many laboratory assessment methods[26] in evaluation of patients with PDPN, electrophysiological testing[27] methods like nerve conduction studies[28] have been regarded as "gold standard" in diagnosis of peripheral neuropathy. Recently, evaluation and quantification of sensory function in neuropathic pain states led to the development of procedures collectively termed as the quantitative sensory testing (QST).[27] It comprises of assessment of light touch using Semmes Weinstein monofilaments or von Frey hairs; vibration testing using calibrated tuning forks; vibration perception thresholds testing using biothesiometer; thermal perception thresholds using a biothesiometer; current perception thresholds using a neurometer; pain thresholds testing using pressure algometer; and thermal pain thresholds testing.[28] Assessment of light touch and temperature sensation indicates small-fiber function whereas vibration sensation indicates large-fiber function.[29] The German Research network[30] on neuropathic pain had established standards and guidelines for use of quantitative sensory testing in patients with neuropathic pain conditions and studies report QST to be better able to detect abnormalities than nerve conduction studies in PDPN patients.[31]

Post-herpetic neuralgia and diabetic peripheral neuropathy have been shown to significantly quality of life in patients.[32] So far, only one

instrument, a self-report measure was shown to objectively assess the quality of life in patients with PDPN, the neuropathy and foot-ulcer specific quality of life instrument developed by Vileikyte et al.[33]

According to the World Health Organization's (WHO) International classification of functioning, disability and health (ICF-DH),[34] evaluation of impairments must be correlated to patient's activity limitations and participation restrictions to holistically address the clinical problem.[35] Hence, measures of impairment in PDPN namely neuropathic pain, neurodynamic findings and sensory findings and their relation to quality of life would enable the clinicians and researchers involved with such patients to understand the complexity of the clinical presentation and the underlying pathogenesis and clinical progression of the disabling condition. Studies relating these measures could not be found in our search thus necessitating current research. The objective of this study was to assess the relationship between neuropathic pain, neurodynamic assessment findings, quantitative sensory testing, and quality of life in PDPN patients.

MATERIALS AND METHODS

Study design: Cross-sectional study with assessor-blinding and random-order testing method.

Ethical clearance: The study's protocol was approved by Institution Ethics Committee of Kasturba Medical College (Manipal University), Mangalore, India and the trial was registered at Clinical Trials Registry- India under universal trial registration number UTRN 052343809-080920102668203.

Study location: Out-patient treatment unit of department of physiotherapy in a multi-specialty teaching hospital.

Patient selection: Patients enrolled in diabetes clinic of the hospital were screened initially for the following inclusion criteria;[36-40]

Known case of type-2 diabetes, with stable glycemic levels (on HbA_1c) for a minimum of six months.

Complaint of bilateral neuropathic pain in the legs and feet (screened using neuropathic pain scale) for a minimum of six months.

Insensitivity to 5-gm monofilament in bilateral feet.

Vibration perception thresholds greater than 25 volts in both feet when assessed using a biothesiometer.

Tested positive on structural differentiation during lower extremity neurodynamic testing on both sides lower limbs. Sciatic neurodynamic test, tibial neurodynamic test and common peroneal neurodynamic test were used for this purpose.

Mechanical allodynia to manual palpation of nerve trunks in bilateral legs and feet. Manual palpation of sciatic, tibial and common peroneal nerve trunks were done for this assessment.

Patients with comorbid musculoskeletal disorders, history of fractures, trauma and surgery to lower limbs, and inability to understand therapist's instructions were excluded.

PATIENT RECRUITMENT

All patients were required to provide a written informed consent prior to their participation in the study. The consecutive patients were randomly assigned to receive either of seven test procedures first. The allocation method was concealed from the primary investigator using sequentially numbered sealed opaque envelopes, generated by computerized table of random numbers method.

OUTCOME ASSESSMENT

Neuropathic pain questionnaire (NPQ)

This self-administered questionnaire was developed by Krause and Backonja,[24] and it consisted of ten items (burning pain, overly sensitive to touch, shooting pain, numbness, electric pain, tingling pain, squeezing pain, freezing pain, unpleasantness and overwhelming nature) and the last two items (increased pain due to touch and increased pain due to weather changes) thus making it twelve items in total. Each of the items was to be scored on a eleven-point visual analogue scale (0-10) with anchors for no

pain and worst pain at both ends. The items with negative discriminant function score were electric pain, squeezing pain, overwhelming nature and influence of weather). The total discriminant function score below zero indicated non-neuropathic pain and score at or above zero indicated neuropathic pain. Of the eight items with positive discriminant function scores, a total score of 80 indicated the intensity or severity of neuropathic pain perceived by the patient.

NEURODYNAMIC ASSESSMENT: NEURODYNAMIC TESTING (NDT)[41]:

Sciatic neurodynamic test- straight leg raise (SLR)$_1$: The examiner passively lifts the tested lower extremity with knee maintained in full extension till the onset of perceived symptoms or a feel of resistance. At that point, structural differentiation maneuver of ankle dorsiflexion or plantarflexion was done to observe for alteration in symptoms. A positive structural differentiation indicated altered neural mobility of the sciatic nerve. *Tibial neurodynamic test- SLR$_2$:* The test is similar to the SLR$_1$ but the ankle dorsiflexion and eversion was performed before the SLR. The structural differentiation was done by hip adduction or internal rotation.

Common peroneal neurodynamic test-SLR$_3$: The test is similar to SLR$_1$ and SLR$_2$, but the ankle movements of plantarflexion and inversion were performed before the SLR component.

The neurodynamic test findings were recorded as positive or negative, depending upon the reproduction of patient symptoms and alteration of symptom responses during structural differentiation.

NERVE TRUNK PALPATION (NTP)[20]:

Sciatic nerve palpation: Sciatic nerve was palpated in the distal margin of the gluteal fold at or near the point between a line connecting greater trochanter and ischial tuberosity, where it exits from the greater sciatic notch.

Tibial nerve palpation: Tibial nerve was palpated in the medial aspect of the distal one-thirds of lower leg where it passes through the tarsal tunnel.

Common peroneal nerve palpation: Common peroneal nerve was palpated at near the fibular head (traced from posterior to anterior distal to the knee laterally) where it winds around the head and travels distally in the upper-third of the leg.

The nerve trunk palpation responses were recorded as positive or negative depending upon the mechanical allodynia provoked on manual palpation and reproduction of patient symptoms along the course of the nerve trunk.

VIBRATION PERCEPTION THRESHOLD (VPT)

The VPT testing was done using Vibrotherm™ Biothesiometer[42] with the probe placed on the subject's skin. The therapist slowly increased the intensity of vibratory stimulus until onset of vibration sense is reported. Minimum intensity of vibration felt as a sensation reported by the subject was taken as the VPT. Both appearance and disappearance of the sensation of vibration were measured. Appearance of vibration was measured by turning up the vibration stimuli until the subject was just able to perceive vibration. Disappearance was measured by increasing the stimuli to above that of the appearance value, and then slowly reducing the stimuli to where the subject no longer felt the stimulus.[43] The therapist who performed the VPT testing using the equipment was trained prior and intra-rater reliability was established in five healthy subjects prior to the study. The ICC was found to be .91.[44] The procedure is then repeated on the other foot by the same therapist. The total contact duration was maintained to be less than 30 seconds to prevent adaptation and interval between two trials was maintained at 4 mins to facilitate recovery of cutaneous mechanoreceptor afferents to vibratory stimulus.[45] Total duration of testing VPT per side was then 10 mins.

THERMAL PERCEPTION THRESHOLD(TPT)- METHODS OF LEVELS (MLE):

The procedure for testing thermal perception thresholds was done as per described by Malanda et al[46] and done earlier by Kumar et al.[44,47] The Methods of Levels (MLE) was used in this study.

MLE is characterized by confirming or denying a well-defined temperature change. Starting from 32°C, temperature rises (warm sensation) or decreases (cold sensation) with a 2°C step (rate of change 1°C/s). Based on the subjects answer ("yes" or "no" sensation) the °C amplitude of the following temperature step is doubled ("no" answer) or halved ("yes" answer) until a minimal perceptive criterion is established. In this "yes/no" procedure post-stimulus speed of reaction and by that reaction time does not play a role. By doing so a complete MLE test consists of several single stimuli resulting in a finally acquired reaction-time free temperature threshold. Anticipation or prediction of stimuli is prevented by random inclusion of "dummies" (no temperature change after the auditory signal) and combining two separate sequences of levels stimuli in a single test sequence. In this study levels thresholds were determined by applying temperature stimuli directly after an auditory cue (change rate 1°C/s). The testing of cold sensation sequence preceded warm sensation. Return to adaptation temperature (32°C) started as soon as participant responded "yes" or "no" (return rate 4°C/s). The inter-stimulus interval was randomized between 4 and 6 s and the minimal perceptive criterion was set to 0.1°C. Final MLE threshold for either cold or warm sensation was considered the mean of the last "yes" and "no" answered temperature step value.

NEUROPATHY-SPECIFIC QUALITY OF LIFE- NEUROQOL

The NeuroQoL developed by Vileikyte et al,[33] is a self-administered questionnaire which questions the presence and frequency of symptoms in the past 4 weeks. The first part has seven questions each of which are scored on a 5-point likert scale from "all the time" to "never." Each question is also accompanied with three options for bothersomeness (very much; some bother; none). The second part has on quality of perceived symptoms. The third part is for weakness, unsteadiness in standing and gait. The fourth part is on influence on work situations and finally on social influence and self-perceived quality of life. Total score ranges from 0-100 where maximum scores indicate worst perceived quality of life.

The outcome measures were taken in random order, (selected by a toss of a coin method) by another physiotherapist who was blinded to study design. Total assessment duration per patient was for one-hour.

DATA ANALYSIS

All correlations were analyzed using Karl-Pearson's correlation co-efficient at 95% confidence interval using SPSS 11.5 for Windows. Spearman's Rho was used for correlating neurodynamic testing and nerve trunk palpation findings. R values for interpretation of correlation were prefixed into four categories as r=0.0-0.3 (weak); >.3 and <.6 (fair); >.6 and <.9 (good); and >.9 (excellent). Secondary analysis was done using one-way ANOVA for comparison of groups based on positive-tested nerves on neurodynamic assessment for difference in the other variables.

RESULTS

Of the total 366 patients screened from August 2007 to September 2009, 112 fulfilled the inclusion criteria. The demographic characteristics of all 112 patients are provided in table-1 and neurodynamic assessment findings were summarized in table-2.

CORRELATION ANALYSES

NPQ versus VPT, HPT, CPT and NeuroQoL:

There was a statistically insignificant weak negative correlation between NPQ score and VPT in volts with r = -.018. NPQ had a fair positive correlation with HPT (r=.436) (figure-1a) and CPT (r=.349) (figure-1b) both of which were statistically significant. NPQ had a statistically significant fair negative correlation with NeuroQoL (r=-.377) (figure-1c).

Table 1: Demographic characteristics of patients in this study

Demographic factor	Descriptive
Age (years)	62.95 ± 6.73
Gender- Male(%) female (%)	 64 (57.1%) 48 (42.9%)
Duration of diabetes (years)	5.74 ± 2.26
Duration of neuropathic pain (years)	3.63 ± 1.62
Neuropathic pain questionnaire	56.50 ± 7.01
Vibration perception threshold (in volts)	45.91 ± 2.15
Heat perception threshold (in degrees Celsius)	16.64 ± 4.01
Cold perception threshold (in degrees Celsius)	16.16 ± 3.38
Neuropathy-specific quality of life	37.24 ± 13.47

Table 2: Neurodynamic assessment findings in the patients

Nerves tested positive, N (%)	Neurodynamic testing	Nerve trunk palpation
Sciatic nerve	3 (2.7%)	0 (0%)
Tibial nerve	15 (13.4%)	10 (8.9%)
Common peroneal nerve	14 (12.5%)	16 (14.3%)
Sciatic + tibial nerve	19 (17%)	15 (13.4%)
Sciatic + common peroneal	7 (6.3%)	4 (3.6%)
Tibial + common peroneal	18 (16.1%)	21 (18.8%)
Sciatic + tibial + common peroneal	36 (32.1%)	46 (41.1%)

Correlation analyses:

NPQ versus VPT, HPT, CPT and NeuroQoL:

(Figure 1a)

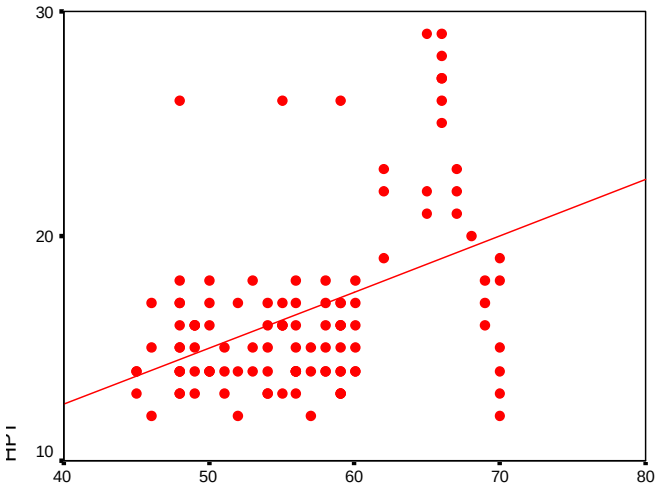
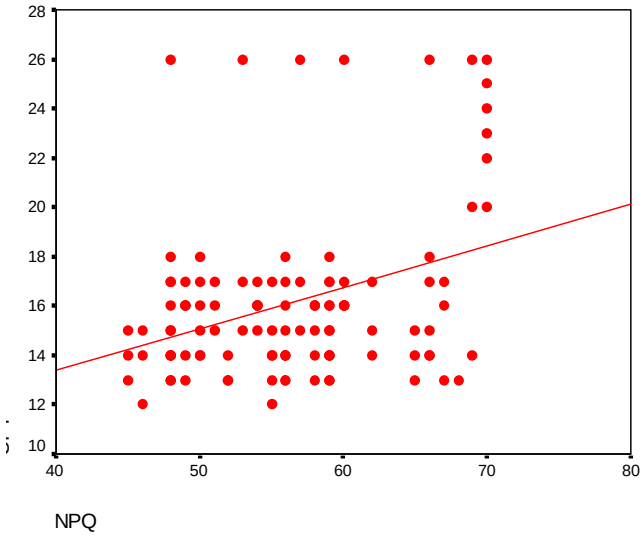


Figure 1b)



(Figure 1c)

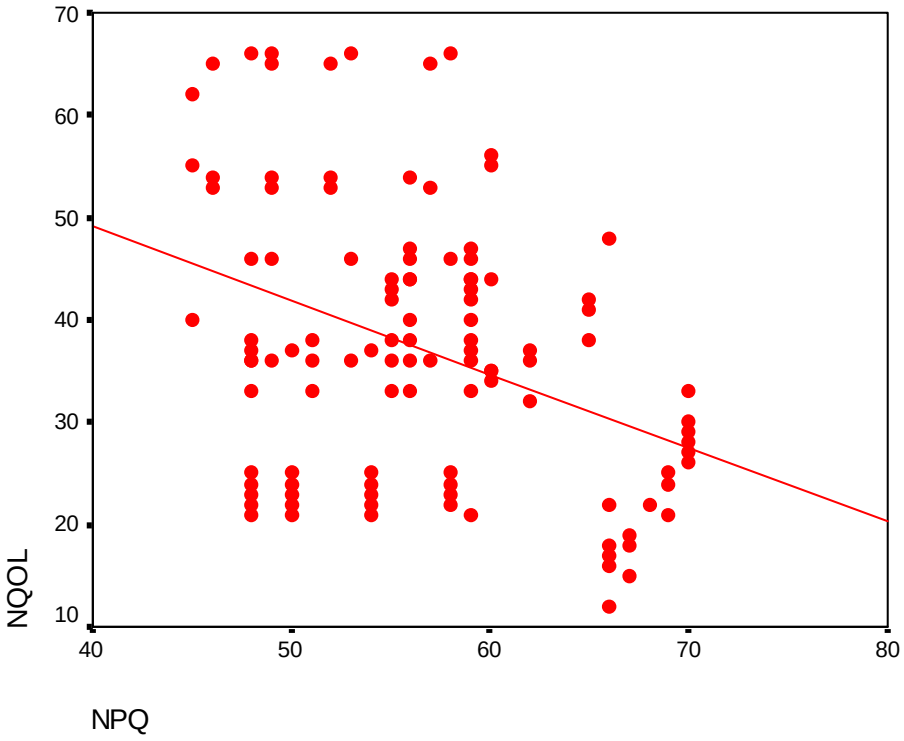
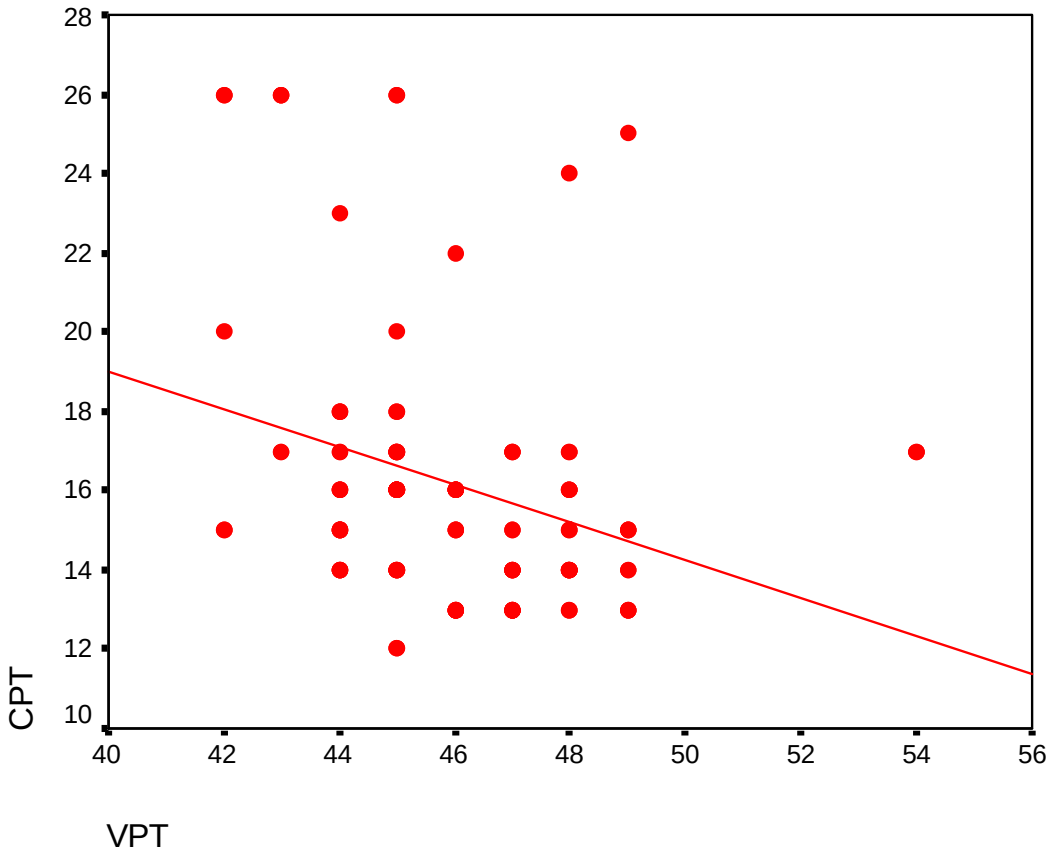


Figure 1a, 1b, 1c: showing scatter plots for correlation between NPQ and HPT, CPT and NQOL respectively.

VPT versus HPT, CPT and NeuroQoL:

VPT had a statistically insignificant weak negative correlation with HPT (r=-.012) and NeuroQoL (r=-.069); and a fair negative correlation with CPT (r=-.304) that was statistically significant (figure-2).

Figure 2: showing scatter plot for fair negative correlation between VPT and CPT



HPT VERSUS CPT AND NEUROQOL

HPT had a weak negative correlation with CPT (r=-.026) and a weak positive correlation with NeuroQoL (r=-.284), the latter was statistically significant.

CPT VERSUS NEUROQO

CPT had a weak negative correlation with NeuroQoL (r=-.054) that was not statistically significant.

NDT AND NTP

Spearman's rho showed statistically significant (p=.000) good positive correlation between NDT and NTP at r=.741.

SECONDARY ANALYSIS

One-way ANOVA showed statistically insignificant differences between the groups based on patients' positive-tested nerves on neurodynamic testing and the other measures (NPQ, VPT, HPT, CPT, and NeuroQoL).

Figure 3a

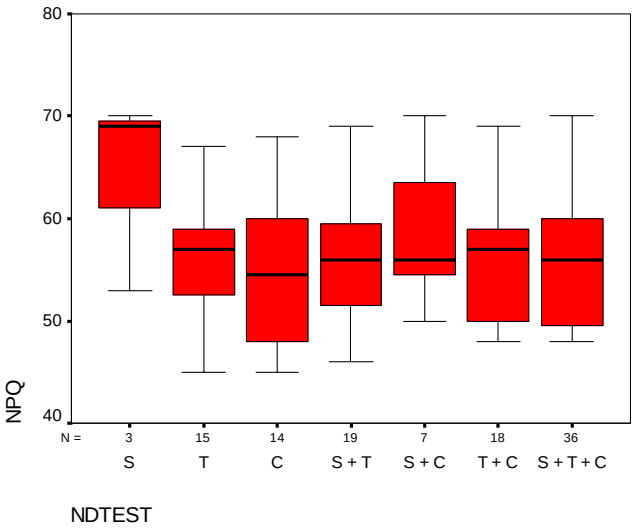


Figure 3b

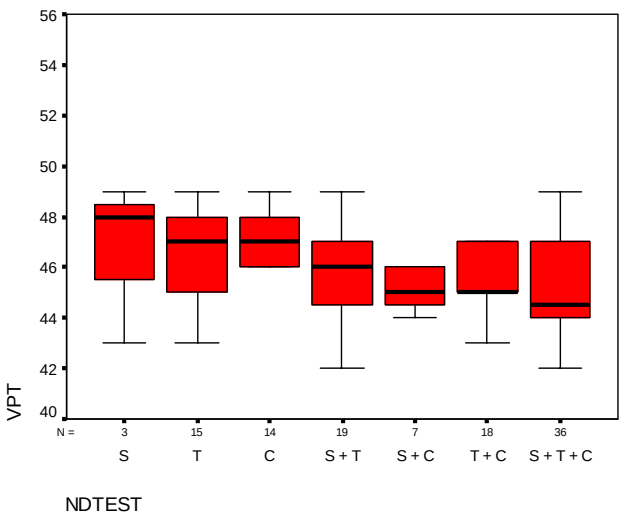


Figure 3c

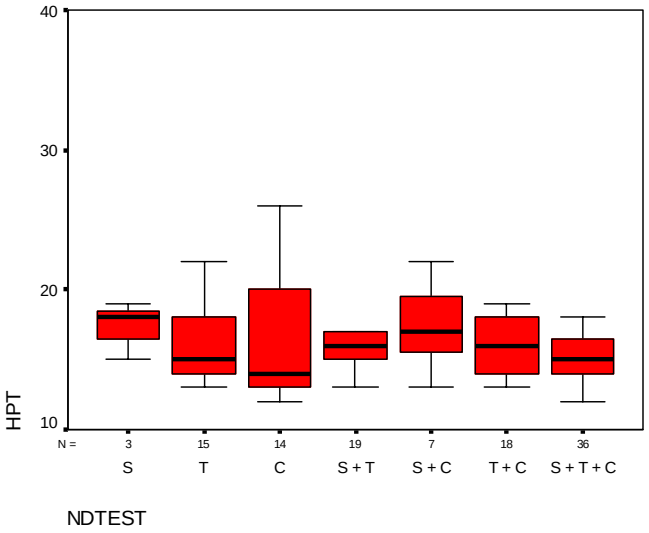


Figure 3d

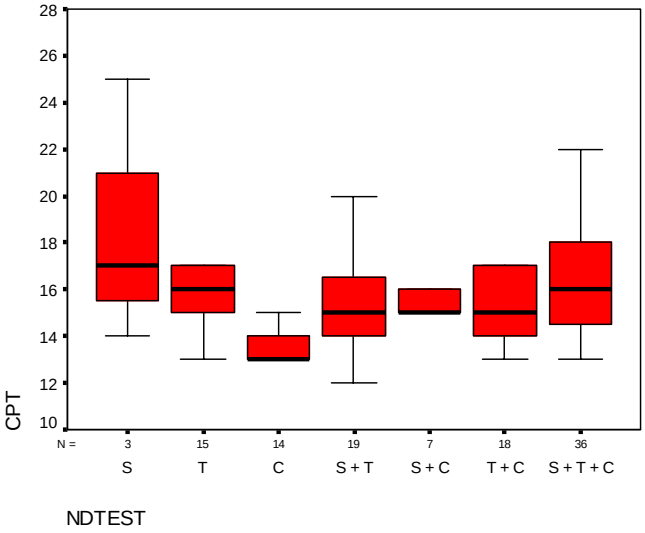
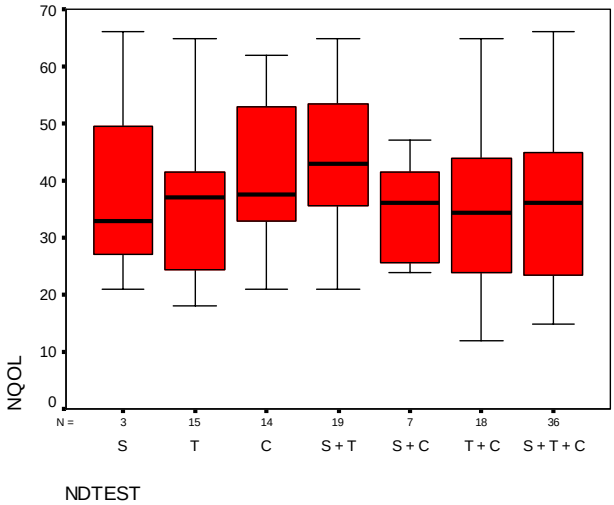


Figure-3e



Figures 3a-e: showing comparison between groups based on positive-tested nerves on neurodynamic testing on NPQ, VPT, HPT, CPT and NQOL respectively.

One-way ANOVA showed statistically significant differences between the patients' positive-tested nerves on nerve trunk palpation and NPQ, VPT and CPT, whereas the differences in HPT and NeuroQoL were not statistically significant. Post-hoc analysis revealed that NPQ scores, VPT and CPT were higher in the group which had all three nerves tested positive on palpation.

Figure 4a

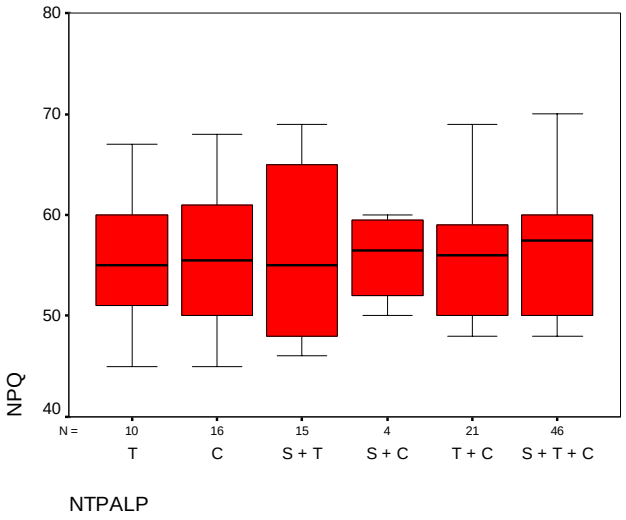


Figure 4b

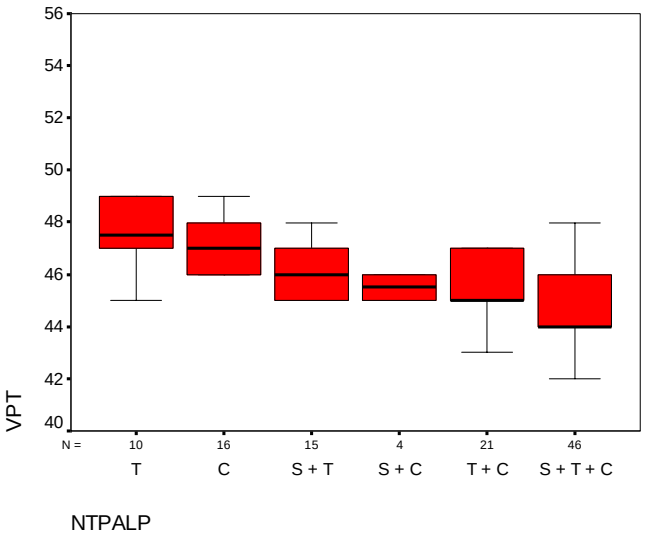


Figure 4c

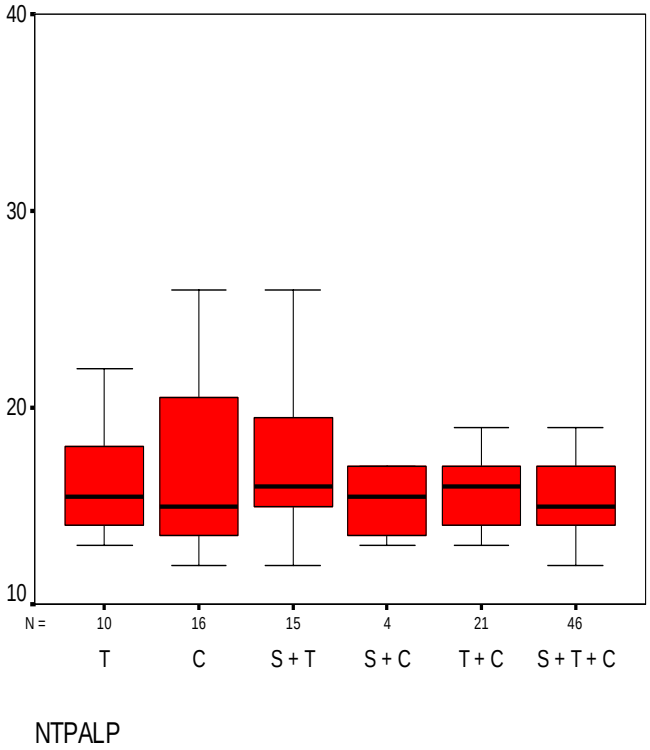


Figure 4d

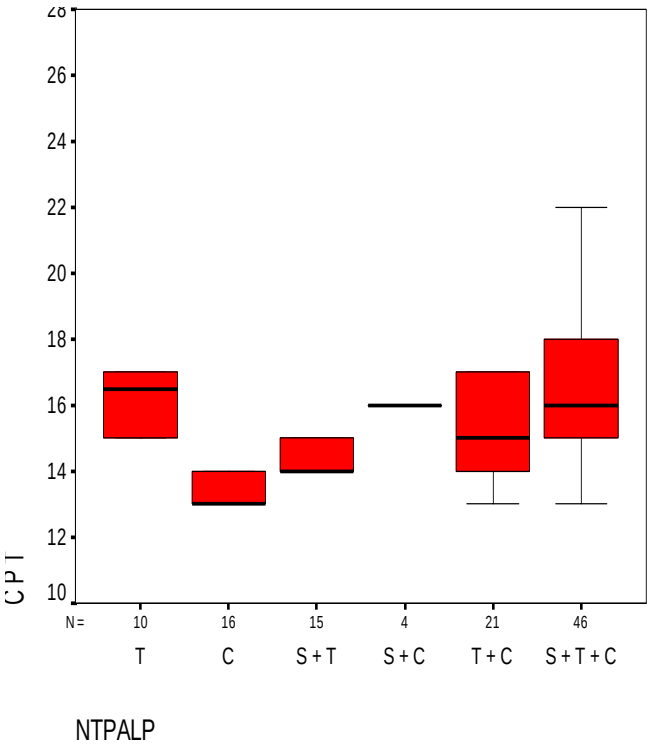
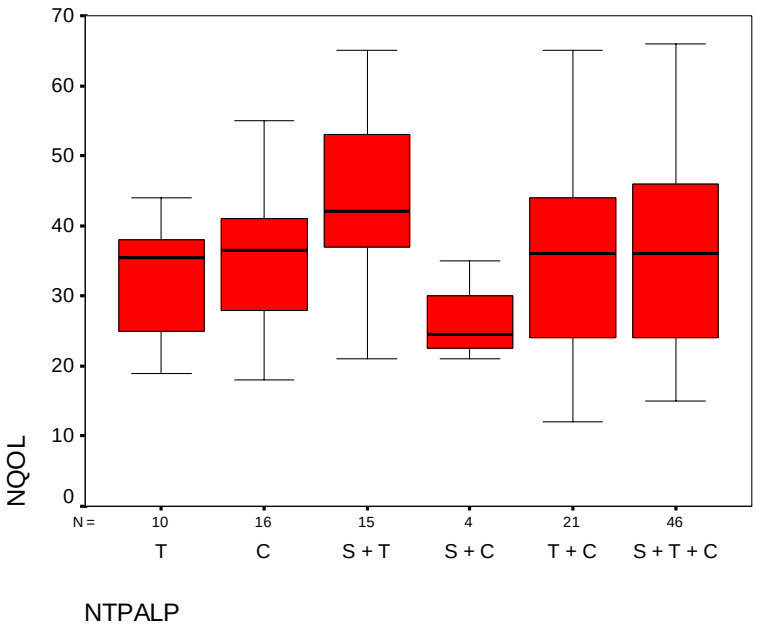


Figure 4e



Figures 4a-e: showing comparison between groups based on positive-tested nerves on nerve trunk palpation on NPQ, VPT, HPT, CPT and NQOL respectively

DISCUSSION

The study showed a good positive correlation between neurodynamic test findings and nerve trunk palpation that is, the nerve tested positive on neurodynamic testing also showed mechanical allodynia on nerve trunk palpation. Though the two procedures assess different properties of mechanosensitivity in symptomatic peripheral nerves, the inter-dependence between neural longitudinal gliding (induced by neurodynamic testing) and transverse gliding (induced by nerve trunk palpation) was well demonstrated. Coppieters and Butler[48] suggested that sliders and tensioners are two different mechanical properties of nerves which could be elicited during neurodynamic test movement components and sliders facilitate neural sliding between nerve and its interface whereas tensioners facilitate intraneural gliding between nerve fascicles and neural connective tissue sheaths.[49] Butler[50] explained activity-specific mechanosensitivity for peripheral nerves and the study thus observed nerve-specific mechanosensitivity in PDPN patients.

We tested the three main nerves of the lower limb affected in diabetic peripheral neuropathy namely the sciatic, tibial and common peroneal nerves. All the nerves have a common component of SLR in their neurodynamic test and the three nerves are connected to each other in that the latter two are branches from the former one.[51] A highly irritable distal nerve could elicit symptoms during testing proximal nerve eg., tibial nerve symptoms could be reproduced during sciatic neurodynamic testing and vice versa. We relied more on the symptom reproduction and structural differentiation during neurodynamic testing than range of motion for our analysis and this reduced objectivity of our findings. Same applied for nerve trunk palpation, where we did not quantify the pressure sensitivity using a pressure algometer as it was earlier used by Walsh et al.[52]

Neuropathic pain scores correlated well with quality of life scores and quantitative sensory testing measures, which suggested that subjective perception of responses and subjective reporting of activity limitations and participation restrictions related well with objective clinical evaluation of sensory perception threshold testing. A well-proven inter-relationship between these measures indicates the predictability of pathogenesis of the disorder and further cohort studies can explain

the causal relationship between the measures in PDPN patients. Understanding of mechanisms of peripheral neuropathic pain would enable effective clinical decision-making and use of appropriate musculoskeletal physiotherapy techniques.[53] Though statistically significant, the strength of correlation found was only fair to good, indicating further studies on larger sample size to have larger observed effects.

VPT values correlated negatively with CPT, which showed that dysfunction in large fibers and small fibers in PDPN were inter-twined and though large fiber dysfunction precedes small fiber dysfunction in DPN, the physiologic function of cutaneous receptors and/or the afferent fibres for these two sensations are yet to be explored. The receptor afferents for vibration sensation are myelinated and include both large diameter (group Aa, diameter 12–20 mm, conduction velocities 72 to 120 m/s) and medium diameter (group Ab, diameter 6–12 mm, conduction velocities 36 to 72 m/s) fibres. Merkel disk receptors respond maximally to low frequencies (5–15 Hz), Meissner's corpuscles to mid-range frequencies (20–50 Hz), and pacinian corpuscles to high frequencies (60– 400 Hz). Humans are most responsive to vibration at frequencies of 200–250 Hz.[54]

The observed lack of relationship between the other measures could be attributable to the rigor in the study design, random order of testing to minimize the influence of sequence of testing or effect of testing a measure on the patients' response to the other test measure. Also, the observed relationship could be due to the disorder only if future case- control studies find association in the outcome measures.

Future studies could be on other neuropathic pain states and correlated with other outcome measures such as real-time diagnostic ultrasound for longitudinal nerve motion,[55] current perception threshold testing for fiber-specific sensory testing, and as longitudinal studies to establish a cause-effect relationship between the related measures.

As we shift from an evidence-based to an evidence-informed paradigm[56] for clinical decision-making, a study as this one added valuable information towards understanding the mechanisms behind patients' symptoms in PDPN. Appropriate clinical reasoning[57] combined with adequate therapeutic skills would provide efficient interventions for relief of symptoms in PDPN patients which have to be studied in future controlled clinical trials.

CONCLUSION

There was a good positive correlation found between NDT and NTP. There was a fair positive correlation found between NPQ and HPT; NPQ and CPT. There were a fair negative correlation found between NPQ and NeuroQoL; VPT and CPT.

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