Original Article

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An Evidence-Informed Assessment and Treatment of Vibration Perception in Diabetic Peripheral Neuropathy

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Abstract

Background: Assessment of vibration sensation is essential for diagnosing large-fiber dysfunction in peripheral neuropathies and is considered as a gold standard for diagnosis of diabetic peripheral neuropathy (DPN), since it can efficiently predict the natural history and progression of the disorder. **Purpose:** To explore the existing evidence for vibration perception in DPN in terms of evidence from published assessment and treatment studies. **Methods:** A systematic review of PubMed using the search terms– 'vibration and diabetic neuropathy' was done to identify articles from 2008 to 2012. The obtained articles were categorized under assessment and treatment studies depending upon their scientific objective. The data were extracted and descriptively synthesized. **Results:** Tuning fork (sensation) and biothesiometry (sensory threshold) was used for diagnosis of vibration sensation. Vibration perception threshold (VPT) had good measurement properties that merit its clinical use in bedside screening as well as population-based estimation of prevalence of DPN. Medical management (hypoglycemic drugs, neurotropic drugs, vasoactive drugs, herbal medicine and acupuncture), electrical and mechanical treatments were shown to influence VPT. VPT had good predictive ability to identify large-fiber dysfunction and impending risk for other comorbidities/ complications of DPN such as foot ulcers and amputations. **Conclusion:** Vibration perception was used as a diagnostic, therapeutic and prognostic tool in DPN.

Keywords: Diabetic peripheral neuropathy; Neurological examination; Sensory evaluation; Large-fiber dysfunction.

Introduction

Diabetic peripheral neuropathy (DPN) affects up to 50% of patients with diabetes and is a major cause of morbidity and increased mortality and its clinical manifestations include painful neuropathic symptoms and insensitivity, which increases the risk for burns, injuries and foot ulceration.[1]

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Diagnostic methods for DPN include clinical (the neuropathy symptom score [NSS], the neuropathy disability score [NDS], vibration perception testing, Tinel's sign and Phalen's sign), laboratory (fasting plasma glucose and glycosylated haemoglobin levels) and electro-physiological (nerve conduction studies, H-reflex and F-wave measurements) methods.[2] Advanced peripheral diabetic neuropathy (PDN) is associated with elevated sensory perception thresholds that progress to sensory loss and degeneration of all fiber types in peripheral nerve.[3]

Quantitative sensory testing (QST) is a method to objectively measure and quantify somatic sensations such a light touch, pressure, pain, thermal (hot/cold), and vibration.[4] QST is considered superior to electrophysiological studies which were previously regarded as gold standard in diagnosis of peripheral neuropathy.[5]

Assessment of vibration sensation is essential

for diagnosing large-fiber dysfunction in peripheral neuropathies.[6] Vibration perception testing is considered as a gold standard for diagnosis of DPN,[7] and it can efficiently predict the natural history and progression of the disorder.[8]

Thus there is need to explore the existing evidence for vibration perception in DPN in terms of assessment and treatment studies and henceforth is based this study's objective to thus provide an evidence-informed update of current research literature.

Methodology

A systematic review using the following search terms was done and entered into PubMed- vibration [Title/Abstract] AND (diabetes [Title] OR diabetic [Title]) AND (neuropathy [Title] OR neuropathic [Title]) with search filters activated for articles with abstracts and published in English language for a five-year period from 2008 to 2012. The search was performed by two testers independently and mutual consensus method was adopted periodically. Two main themes were selected under assessment and treatment of vibration sensation.

Results

Initially, 54 studies were identified and upon scrutiny of citations and their abstracts, 17 were excluded since they were primarily not on vibration, and a final list of 37 studies were considered for data extraction and synthesis into three categories- diagnostic, therapeutic and prognostic use of vibration sensation in DPN.

Vibration Perception Used as a Diagnostic Outcome Measure (Screening Criterion) for DPN

Types of Vibration Testing and Test Interpretation

Presence or absence of vibration sensation tested using a 128-Hz tuning fork was used conventionally in few studies.[9,10,11,12,13] Much later, VPT >2 SD from the predicted mean for the patient s age was used in few studies,[14,15] VPT>20V was used as the cut-off for diagnosing DPN in some studies[16,17,18] whilst 25V cut-off was used in many studies.[19,20,21,22,23]

Measurement Properties

Ghosal *et al*[24] computed the normative data of VPT, compared results of VPT among type 2 diabetes patients with and without neuropathy, validated VPT taking NDS [Neuropathy Disability Scores] as gold standard and suggested a cut off value for the Indian population on 50 T2DM patients. The normative data of VPT for mean of 4 sites (malleoli and great toe) was found to be 11.3±4.9mV. The VPT value was also higher among diabetic patients with neuropathy compared to non-neuropathic and non-diabetic patients. Lowering the cutoff value of VPT from 25mV to 20mV increased the sensitivity from 50% to 62.5% in detecting diabetic neuropathy.

Kanji *et al*[9] systematically reviewed the literature to determine the clinical examination findings predictive of asymptomatic large-fiber peripheral neuropathy (LFPN) in DPN and found 9 studies on diagnostic accuracy and 3 studies on precision. The most useful examination finding was vibration perception testing with a 128-Hz tuning fork (LR range, 16-35) and a normal result on vibration testing (LR range, 0.33-0.51) made LFPN less likely.

Martin *et al*[15] determined the sensitivity, specificity, positive predictive value, and negative predictive value of vibration perception threshold (VPT) testing in 1,177 adult subjects with type 1 diabetes and found that VPT was a sensitive measure of confirmed clinical neuropathy (87%) and of definite clinical neuropathy (80%) and a specific measure of abnormal nerve conduction (62%). Higher VPT cut points improved test sensitivity and lower cut points improved

specificity. Areas under the receiver operating characteristic curves ranged from 0.71-0.83 and were higher for older than for younger subjects and highest for those with confirmed clinical neuropathy.

Papanas *et al*[23] compared the new indicator test for sudomotor function (Neuropad) with the vibration perception threshold (VPT) and the clinical examination in the diagnosis of peripheral neuropathy in 154 subjects with type 2 diabetes. Both the indicator test and the VPT had a high sensitivity for neuropathy. Sensitivity is higher with the indicator test, but specificity is higher with VPT.

Prevalence Studies of DPN

Liu *et al*[11] investigated the prevalence of diabetic peripheral neuropathy by combining two methods-the 10-g Semmes-Weinstein monofilament and 128-Hz tuning fork examinations in 1193 patients, including 1067 known cases of diabetes (KDM group) and 126 newly diagnosed cases of diabetes (NDM group). Screening results showed that the prevalence of perception defects was 17.02% in the total population, 18.28% in the known DM group and 6.35% in the new DM group, respectively.

Lu *et al*[22] determined the prevalence of DPN in 435 type 2 diabetic patients, and 59.1% had vibration perception threshold > or =25 V. Rani *et al* (2010) estimated the prevalence of diabetic neuropathy (severity wise) using VPT where the severity of neuropathy was graded into three groups based on VPT score as mild (20-24.99 V), moderate (25-38.99 V), and severe (e"39 V). The overall prevalence of diabetic neuropathy was 18.84%, mild diabetic neuropathy was 5.9%, moderate diabetic neuropathy was 7.9%, and severe diabetic neuropathy was 5%.

Vibration Perception Used as a Therapeutic Outcome Measure (Intervention Studies) in DPN:

Medical Management

Hypoglycemic Drugs: Callaghan *et al*[25] examined the evidence for enhanced glucose control in the prevention of distal symmetric polyneuropathy in people with DM in their systematic review of 17 randomized controlled studies which included quantitative vibration testing as a secondary outcome, and found that intensive treatments favorably influenced VPT values in both types of DM.

Charles *et al*[26] evaluated the effects of multifactorial treatment (IT) of type 2 diabetes in primary care on the prevalence of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) 6 years later in a pragmatic, cluster-randomized parallel group trial and found that in participants tested for vibration detection thresholds, the prevalence of a least one abnormal test was 34.8% (26.7-43.0) in the routine care (RC) arm and 30.1% (24.1-36.1) in the IT arm.

Dziemidok *et al*[10] assessed the association between glycemic control using glycated haemoglobin level and indices of diabetic neuropathy which included a 128 Hz calibrated tune-fork for the vibration perception test in 204 patients with diabetes (type 1 - 29; type 2 - 175). About 30% of patients had decreased sensation of vibration and they neither had significantly higher (Neuropathy Syndrome Total Score, temperature sensation disturbances) nor significantly lower (vibration and touch), glycated haemoglobin levels compared to patients without neuropathy.

Neurotropic Drugs: Fonseca *et al*[20] determined whether a combination of L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate (LMF-MC-PLP [Metanx; Pamlab LLC, Covington, La]) improved sensory neuropathy in their multicenter, randomized, double-blind, placebo-controlled trial involved 214 patients with type 2 diabetes and neuropathy, who were randomly assigned to 24 weeks of treatment with either Mentax or placebo and there was no significant effect on VPT post-treatment.

Sharma and Sharma[27] evaluated efficacy of Epalrestat, an aldose reductase inhibitor on

2000 patients with diabetic neuropathy, who were treated for 3-12 months, and analyzed the subjective symptoms (spontaneous pain, numbness, coldness and hypoesthesia) and the nerve function tests (motor nerve conduction velocity, sensory nerve conduction velocity and vibration threshold). The study found improvement rate of the subjective symptoms to be 75% (slightly improved or better) and that of the nerve function tests 36%.

Talaei *et al*[28] compared the efficacy of parenteral vitamin B(12) and nortriptyline, for symptomatic improvement of pain, paresthesia, burning, freezing, stabbing and electrical sensation in 100 patients (50 in each group) and found no changes in vibration, position, pinprick and nerve conduction parameters in both groups post-treatment.

Vasoactive Drugs: Jude et al[29] investigated the effect of L-arginine on endothelial function, transcutaneous oxygen and clinical neuropathy in 30 patients with DPN who were randomized to receive L-arginine (3 g three times daily) or placebo (3 g three times daily) for 3 months. No difference was observed in VPT, which suggested that L-arginine has no effect on clinical neuropathy.

Laczy *et al*[30] examined the efficacy of pentoxifylline (PF) and pentosan polysulphate (PPS) combination therapy (infusions 100-100 mg/day for 5 days) versus placebo (saline infusions) on diabetic neuropathy and nephropathy in 77 and 12 type 2 diabetic patients respectively. Vibration threshold values, an indicator of the loss of sensory nerve function, were found to be improved after therapy.

O'Donnell *et al*[31] assessed the effects of cilostazol on VPT in 26 diabetic patients with peripheral arterial disease (PAD) at baseline, 6 weeks, and 24 weeks, and found no significant difference between the treatment groups post-intervention.

Complementary and Alternative Medicine

Herbal Medicine: Bakhshayeshi *et al*[32] evaluated of effect of Semelil (ANGIPARS™), a new herbal drug for treatment of diabetic foot ulcers or diabetic peripheral neuropathy in 49 type 2 diabetes patients with different degrees of neuropathy who were evaluated in two groups (ANGIPARS™ and placebo groups) and found that VPT values improved after 12-weeks intervention.

Patel *et al*[33] studied the effects of Bhumyamalaki (Phyllanthus niruri) and Atibala (Abutilon indicum) on 33 patients of diabetic neuropathy who were given Bhumyamalaki Churna 3 g twice a day and decoction of 10 g of Atibala-mula twice a day for 30 days. Changes in numbness, tingling, burning sensation and pain in lower limbs occurred with reversal of sensory perception, with significant reduction of symptoms.

Acupuncture: Tong *et al*[34] investigated the effects of acupuncture on 42 active versus 21 sham-treated cases of DPN on two measures of sensory function that included VPT which showed significant improvement between the groups in favor of the acupuncture group.

Electrical Modalities

Bosi *et al*[35] evaluated the efficacy and safety of 10 sessions of transcutaneous frequency-modulated electromagnetic neural stimulation (frequency rhythmic electrical modulation system, FREMS) to 54 patients or placebo to 56 patients, administered within 3 weeks, 3 months apart, with an overall follow-up of about 51 weeks as a treatment for symptomatic peripheral neuropathy in patients with diabetes mellitus. Non-significant improvements in VPT were observed between groups in favor of FREMS group.

Lavery *et al*[17] determined the efficacy of 90-day anodyne monochromatic infrared photo energy (MIRE) in-home treatments (40 min daily) in 60 individuals with diabetes who were randomly assigned into two treatment groups: active or sham treatment. There were no significant differences in VPT, and other measures in active or sham treatment groups post-treatment, which suggested that

Anodyne MIRE therapy was no more effective than sham therapy in the treatment of sensory neuropathy in individuals with diabetes.

Mohariæ and Burger[36] determined the efficacy of TENS administered three consecutive hours a day for 3 weeks on forty-six patients with painful diabetic neuropathy and the treatment effect was evaluated with cold, warm, cold pain and heat pain thresholds, vibration perception thresholds and touch perception thresholds. After the TENS therapy, there were no changes in cold, warm, cold pain, heat pain, vibratory perception and touch perception thresholds.

Mechanical Modalities

Cloutier *et al*[37] examined the effect of 1 hour of continuous stochastic resonance (SR) stimulation- a subsensory level of mechanical noise presented directly to sensory neurons on sensory nerve function in twenty diabetic patients were studied. The effect of stimulation was measured using VPT at 2 time points, at the beginning and after 60 minutes of continual SR stimulation; at the big toe under 2 conditions: a null (no SR) condition and active SR, defined as mechanical noise below the subject's own threshold of perception. SR for a continuous 60-minute period sustained the VPT improvement in diabetic patients with moderate to severe neuropathy which permitted the conclusion that there was no short-term adaptation to the stimulation signal.

Vibration Perception as a Prognostic Outcome Measure (Predicting Risk Factors) in DPN

Elliott *et al*[14] assessed 1,407 patients with type 1 diabetes and a normal VPT participating in the EURODIAB Prospective Complications Study where VPT was measured using biothesiometry on the right big toe and medial malleolus with an abnormal result defined as >2 SD from the predicted mean for the patient s age. The study found associations of abnormal VPT with an increased incidence of gangrene, amputation, foot ulceration, leg bypass or angioplasty, and mortality. Duration of diabetes and A1C significantly influenced the incidence of abnormal VPT. A previous history of CVD doubled the incidence of abnormal VPT. The study findings indicated that cardiovascular risk factors predicted development of large-fiber dysfunction, which may account for the high mortality rate in patients with an abnormal VPT, and emphasizes the importance of early determination of VPT to detect subclinical neuropathy and to address cardiovascular risk factors.

Kärvestedt *et al*[38] assessed associations between peripheral sensory neuropathy (PSN) found using neurothesiometry, and other diabetes-related complications in a cohort of 156 subjects and the prevalence of PSN increased with severity of retinopathy. Vibration perception threshold was higher in subjects with retinopathy. PSN was more common in subjects with overt nephropathy, with higher vibration perception thresholds, than in subjects without overt nephropathy. PSN was independently associated with PVD, age, male sex, and HDL cholesterol and tended to be independently associated with IGF-1 binding protein but not with diabetes duration or A1C.

Miscellaneous-Vibration Used as an Intervention

Hijmans *et al*[39] investigated the effects on standing balance of random vibrations applied to the plantar side of the feet by vibrating insoles in 17 subjects with neuropathy and 15 nondisabled subjects in four different conditions (eyes open or closed and with or without an attention-demanding task [ATD]), who stood for 60 s on vibrating insoles placed on a force plate. During each condition, the insoles were turned on for 30 s and off for 30 s (random order). Vibrating insoles were shown to improve standing balance in subjects with neuropathy only when attention was distracted.

Discussion

This study aimed to perform an evidence-informed update on assessment and treatment of vibration perception in people with DPN and the evidence found was insufficient to provide concrete recommendations to suit clinical practice. Vibration testing is not only used in neurological examination but also in musculoskeletal examination.[40] The wide applicability of testing vibration thus implies equally wider perspective of assessment and interpretation of test findings from an evidence-informed biopsychosocial domain.[41]

Most of the included studies utilized one or more sites of measurement such as great toe or medial malleolus, whereas other reports suggested fifth metatarsal and ankle so as to identify foot at risk for ulceration and other complications.[42]

QST is based upon well-developed psychophysical methods that defined not only the stimulus (type, characteristics, quantity, presentation, testing format, and environment) but also the response (form and analysis).[43] Most of the reviewed studies emphasized the stimulus bot not the responses to testing in DPN which is open for further investigation. One such method of response analysis is the vibration threshold (VT) which equals the mean of vibration perception threshold and the vibration disappearance threshold[44] was not yet studied and/or reported in DPN.

Very few studies on measurement properties highlight the deficiency in diagnostic studies since only moderate inter-observer reliability was reported for VPT assessments in other populations,[45] which indicate future studies in DPN prior to extrapolation.

There existed immense influence of anthropometric factors such as age, sex and height of the individual, and the testing room temperature on vibration perception.[46] Not many studies on DPN had explored these inter-relationships of vibration sensation with such factors which is again yet to be answered in future studies.

Future assessment studies should establish relationships between vibration perception and clinical examination findings,[47] neuropathic pain,[48] clinical assessment scores,[49] neurodynamic examination findings[50] and quality of life[51] in people with DPN and future treatment studies should establish the effects, efficacy and effectiveness[52] of medical,[53] surgical,[54] physiotherapeutic,[55] neurodynamic[56] and acupuncture[57] treatment methods with regards to improvements in vibration perception.

Conclusion

Vibration perception was used as a diagnostic, therapeutic and prognostic tool in DPN. Tuning fork (sensation) and biothesiometry (sensory threshold) was used for diagnosis of vibration sensation. VPT had good measurement properties that merit its clinical use in evaluation of prevalence of DPN. Medical management (hypoglycemic drugs, neurotropic drugs, vasoactive drugs, herbal medicine and acupuncture), electrical and mechanical treatments were shown to influence VPT. VPT had good predictive ability to identify risk for large-fiber dysfunction and other comorbidities of DPN.

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