Quantitative sensory testing in type 1 diabetic patients with painful and painless diabetic neuropathy

Ahmed T. Alahmar

Abstract

The mechanism underlying the development of painful diabetic neuropathy (DN) is unknown. The aim of this study was to compare quantitative sensory testing (QST) characteristics of patients with painful and painless DN and to correlate QST measures with DN pain. 50 type 1 diabetic patients with DN (30 with painful DN and 20 with painless DN) and 32 age-matched non-diabetic controls were included in this study. For all patients and controls, a detailed assessment of DN was performed which comprised McGill visual analog scale (McGill VAS) for pain, neuropathy symptom profile and neuropathy disability score, QST in form of cold thresholds (CT), warm thresholds (WT), and vibration perception thresholds (VPT), nerve conduction studies (NCS), deep-breathing hear rate variability (DB-HRV), and Neuropad staining scores. Measures of QST, NCS, and DB-HRV were correlated with McGill VAS scores for pain. Apart from NCS, there were no significant differences in CT, WT, and VPT, DB-HRV and Neuropad scores between patients with painful and painless DN. Cold threshold ($r = -0.57$, $P = 0.005$), warm threshold ($r = 0.47$, $P = 0.026$), and DB-HRV ($r = 0.50$, $P = 0.023$), however, correlated significantly with McGill VAS scores of pain. In conclusion, QST is a helpful tool to identify small nerve fibers damage of DN, correlates with pain intensity but cannot differentiate between painful and painless DN. Both central and peripheral neural injury could be implicated in the genesis of DN pain.

Introduction

Diabetic neuropathy (DN) is one of the most common debilitating complications of diabetes mellitus affecting around 30-50% of patients (1). It presents as paradox where at one end there are patients with painful symptoms, while at the other end, there are patients with complete loss of sensation. Painful symptoms exist in up to 50% of patients with DN (2) and defined as pain arising as a direct consequence of abnormalities in the somatosensory system in people with diabetes (3). The development of pain in patients with DN imposes significant impact of the quality of life and raises major treatment challenges.

Different mechanisms have been proposed for DN pain which encompass peripheral and central sensitization, altered expression and distribution of sodium and calcium channels on affected neurons including posttranslational modification, sympathetic sprouting, reduction in the inhibitory signals of nociception, altered neuropeptide expression, and damage to small fibers (3-5). The exact mechanism of DN pain, however, is unknown.

Unfortunately, the lack of predictors of DN pain together with seasonal, social, and daily activity variability in the intensity of pain create difficulties in the quantification of DN pain (4,6). Validated scales for the quantification of DN pain include modified pain inventory, the Leeds assessment of neuropathic symptoms.
and signs pain scale, and McGill pain questionnaire which is simple visual analog scale (VAS) with (0-10) rating of pain (3,7,8). Different tests have been used for DN assessment including nerve conduction studies (NCS), quantitative sensory testing (QST) and tests for autonomic neuropathy. However, there are limited data on the capacity of these tests to differentiate between painful and painless DN. It is also unknown why some patients with DN develop pain while others remain free of pain. Recent studies have linked painful DN to small nerve fibers damage (9). Establishing a reliable diagnostic tools and criteria for small fiber disease is essential as damage to these small fibers could represent the early stage of DPN in which both clinical features and NCS findings are inconclusive. Damage to these small fibers is invisible to NCS but can be assessed by QST (10). With QST, different sensory modalities can be quantified including thermal, vibration, and pain thresholds (11). Application of QST tests can identify a group of patients with different pathophysiological alterations of neurons such as those with deafferentation or those with irritable nociceptors (2,12). Recent evidence shows that there are different subgroups of patients with DN pain using QST and that these subgroups could be used to test the efficacy of different pharmacological therapies (6). Recently, normative data sets of QST have been published for a large population of age- and gender-matched control groups (13). Small nerve fiber damage can be also assessed on nerve biopsy (14), skin biopsy, and recently corneal confocal microscopy (15). Limitations of these tests, however, include invasiveness and the need for expensive equipment and special expertise.

The mechanism underlying the genesis of pain remains elusive, and few studies have explored the QST characteristics of patients with painful and painless DN. The aim of this study was to compare QST characteristics of patients with painful and painless DN and to correlate QST measures with DN pain.

Materials and Methods

Fifty type 1 diabetic patients with DN (30 with painful DN and 20 with painless DN) and 32 age-matched non-diabetic controls were included in this study. All the patients were recruited from Manchester Diabetes Centre, Manchester, UK, while controls were either healthy volunteers or relatives of the patients. The study was conducted at Manchester Royal Infirmary/Wellcome Trust Manchester Clinical Research Facility, Manchester, UK. All participants were provided with information sheet of the study, and they provided informed consent to participate in the study in adherence to the declaration of Helsinki. The study protocol was approved by Central Manchester Ethics Committee.

Patients and controls underwent a set of clinical and biochemical tests including systolic and diastolic blood pressure measurement, body mass index (BMI), HbA1c, estimated glomerular filtration rate (eGFR), and lipid profile using locally approved protocols. DN was defined according to the Toronto consensus (16) as the presence of abnormal personal motor nerve conduction velocity (<42 m/s) and the presence of abnormal symptoms and signs of DN (neuropathy disability score [NDS] score >2). Exclusion criteria comprised the presence of systemic disease, absent pedal pulses, or non-DN. Assessment for DN involved a series of validated neurophysiological tests using previously published methods (17,18). Symptoms and neurological impairment of DN were evaluated with neuropathy symptoms profile (NSP) and NDS, respectively. Painful symptoms of DN were quantified with McGill VAS (McGill VAS) with (0-10) rating of pain where 0 indicated no pain and 10 indicated the worst possible pain. QST involved the assessment of vibration perception threshold (VPT) on the tip of left big toe using neuroesthesiometer (Horwell, Scientific Laboratory Supplies, Wilford, UK). Warm thresholds (WT) and cold thresholds (CT) were quantified on the dorsum of foot opposite to middle metatarsal bones using Neuro Sensory Analyzer TSA-II (Medoc Ltd., UK) with initial limb temperature of 30-32°C. Method of limits was applied for the test where thermal stimulus was gradually increased until patient indicated that the stimulus is uncomfortable. Three measurements were obtained for each test, and the average value was recorded. NCS were performed by consultant neurophysiologist using Medtronic Keypoint™ EMG system. Left Sural and Peroneal nerves amplitudes and velocities were recorded according to standardized protocol. Skin temperature was maintained at 32-35°C to optimize results. Assessment of autonomic function was performed by quantifying deep-breathing heart rate variability (DB-HRV) using a CASE IV machine (WR medical electronics, MN, USA). Plantar sweat glands sudomotor function was evaluated using chromatic indicator Neuropad (Trigocare, Germany). The indicator is blue and changes to pinkish under effect of sweat.
**Statistical analysis**

Results were analyzed using GraphPad Prism v.6.01 for Windows software (GraphPad Software, Inc, CA 92037 USA). Data normality was assessed with Shapiro-Wilk test and/or histograms. Results were expressed as mean±standard deviation and analysis of variance (ANOVA) with Tukey test was used as a post hoc test to compare means among different groups. Unpaired Student t-test was applied to compare mean duration of diabetes between patients groups. Correlations between McGill VAS scores and QST measures, VPT and NCS were performed with Pearson’s correlation coefficient. A level of significance of P < 0.05 was adopted.

**Results**

In this study, duration of diabetes and glycemic control as indicated by HbA1c levels were comparable between patients with painful and painless DN (Table 1). For all clinical and biochemical tests performed, there were no statistically significant differences between patients with painful and painless DN. Systolic blood pressure (P < 0.01) and serum cholesterol were higher, and eGFR (P < 0.001) and low-density lipoproteins (LDL) (P < 0.001) were lower in patients as compared to controls.

The results of DN assessment of patients and controls are summarized in Table 2. As compared to patients with painless DN, those with painful DN demonstrated significantly higher NSP scores (P < 0.05) and lower sural nerve amplitudes and velocities and lower peroneal nerves amplitudes and velocities (P < 0.001). As for QST, VPT were higher in patients with painful symptoms as compared to painless DN, but it was not statistically significant (30.3 ± 13.0, 23.2 ± 15.0°C, respectively). CT (14.8 ± 11.1, 16.4 ± 10.4°C, respectively) and WT (45.0 ± 4.94, 44.3 ± 5.16 °C, respectively) were comparable between patients with painful and painless symptoms. There were also no differences in DB-HRV and Neuropad staining score between patients with and without painful DN. As expected, all DN assessment tests were significantly different in patients as compared to controls.

The correlations between McGill VAS scores and QST and DB-HRV findings are shown in Figure 1. There was statistically significant direct correlation between WT and McGill VAS score (r = 0.47, P = 0.026) as well as significant inverse correlation between CT and McGill VAS score (r = −0.57, P = 0.005). Scores of McGill VAS also correlated directly and significantly with DB-HRV (r = 0.50, P = 0.023). There was no statistically significant correlation between VPT and McGill VAS (r = −0.09, P = 0.66). Both sural (r = −0.25, P = 0.30) and peroneal (r = −0.31, P = 0.14) nerves conduction velocities showed no significant correlations with McGill VAS scores.

**Discussion**

Painful DN is a distressing complication that significantly affects daily activity and quality of life of diabetic patients. Moreover, current available therapies are not effective in all patients or may be associated with...
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Table 2: Diabetic neuropathy assessment in controls and patients with painful and painless diabetic neuropathy

| Parameter | Control | Painless DN | Painful DN | P value       |
|-----------|---------|-------------|------------|---------------|
| Number    | 32      | 20          | 30         |               |
| NSP (0-37) | 0.06±0.24 | 3.32±3.20 | 11.0±6.52 | <0.001        |
| NDS (0-10) | 0.32±0.80 | 6.79±2.39 | 7.13±2.45 | <0.001        |
| McGill VAS (0-10) | 0.0±0.0 | 0.0±0.0 | 6.08±2.77 | NS            |
| VPT R (V)  | 4.95±3.61 | 23.2±15.0 | 30.3±13.0 | <0.001        |
| CT(°C)     | 28.4±2.55 | 16.4±10.4 | 14.8±11.1 | <0.001        |
| WT(°C)     | 36.9±2.39 | 44.3±5.16 | 45.0±4.94 | <0.001        |
| SA (μV)    | 21.0±9.50 | 11.9±6.93 | 3.61±4.22 | <0.001        |
| SNCV (m/s) | 5.10±6.67 | 4.5±5.21 | 3.5±7.26 | <0.001        |
| PA (m/s)   | 5.64±2.03 | 3.88±1.80 | 1.10±1.31 | <0.001        |
| PMNCV (m/s) | 49.1±3.86 | 42.8±5.18 | 30.8±9.29 | <0.001        |
| DB-HRV (beats per min) | 32.6±12.6 | 16.5±18.9 | 12.0±10.9 | <0.001        |
| Neuropad R (%) | 85.6±25.5 | 51.9±43.6 | 47.5±38.7 | <0.001        |

Results are expressed as mean±SD. Statistically significant differences using ANOVA test: †P<0.001. Post-hoc (Tukey test) results significantly different from control subjects, Post-hoc results significantly different from painless neuropathy group. NS: Not Significant (P>0.05); DN: Diabetic neuropathy; NSP: Neuropathy symptom profile, McGill VAS, NDS: Neuropathy disability score, VPT: Vibration perception threshold, WT: Warm threshold, CT: Cold threshold, CIP: Cold-induced pain, HRV-DB: Heart rate variability to deep breathing, SA: Sural nerve amplitude, SNCV: Sural nerve conduction velocity, PA: Peroneal nerve amplitude, PMNCV: Peroneal motor nerve conduction velocity, McGill VAS: McGill visual analog scale, SD: Standard deviation.

Figure 1: Correlations of McGill visual analog scale of pain with quantitative sensory measures and deep-breathing heart rate variability in patients with painful and painless diabetic neuropathy. r, Pearson’s correlation coefficient; McGill VAS: McGill visual analog scale, CT: Cold threshold, WT: Warm threshold, VPT: Vibration perception threshold, DB-HRV: Deep-breathing heart rate variability.
significant adverse effects (19) and this could be attributed to the lack of understanding of the exact underlying mechanism. In this study, duration of diabetes and HbA1c levels were comparable between patients with painful and painless DN albeit HbA1c levels were higher than the recommended values for diabetic patients. While improved glycemic control has been shown to reduce DN, unfortunately, there are no published clinical trials that indicate similar effect for painful DN (10). Similarly, blood pressure, BMI, eGFR, and lipid profile were indifferent between painful and painless DN groups. While there have been recognized risk factors for DN, risk factors for DN pain are more obscure although previous work suggested some risk factors such as obesity, abnormal lipid profile, and peripheral vascular disease (20). Nevertheless, our results do not support contribution of these variables for the development of painful DN. Systolic blood pressure and serum cholesterol were higher, and eGFR and LDL were lower in patients as compared to controls, and these findings have been observed previously in patients with DN (18,17).

Clinical measures of DN (NSP and NDS) were higher in patients with painful DN as compared to painless DN in the present study although only NSP difference was significant. These findings are in agreement with those of another study which detected higher scores of these measures in patients with painful DN, but the study did not observe any differences in QST or NCS tests between patients groups (21). QST measures (VPT, CT and WT) deteriorated in patients with DN as compared to controls, but there were no significant differences between patients with painful and painless DN. These findings are consistent with previous studies by us (17,22) and other researchers (15,23) which reported higher VPT and WT and lower CT in DN patients as compared to controls indicating impaired small nerve fibers function in diabetic patients. These results are also congruent with those of a study conducted on 122 diabetic patients and reported no difference in vibration and thermal thresholds in painful and painless DN groups (21). Moreover, Kramer et al. reported no differences in VPT, CT, and WT in patients with painful and painless DN and suggested that DN pain could be due to structural damage and deafferentation of small nerve fibers in painful DN group (4).

Assessment of QST has been recommended for the diagnosis of small fiber neuropathy in diabetic patients (11), and advantages include accurate control of stimulus and assessing different modalities at different anatomical locations (24). Moreover, unlike intraepidermal nerve fibers (IENF) assessment, QST is non-invasive procedure. There still are some limitations, however, for QST tests which comprise inability to differentiate between peripheral and central neural deficits and being affected by cognitive impairment of patients (9). Lack of the difference in QST measures between painful and painless group may indicate generalized neural injury in these patients and both central as well as peripheral mechanisms participate in the pathogenesis of neuropathic pain in these patients. Maier et al. recently identified five subgroups of DN pain using QST and suggested that they can be used to develop mechanism-based classification of DN pain that can be used to test different potential therapies in these subgroups (13).

Both sural and peroneal NCS measures were lower in patients with painful DN in comparison to painless DN groups. These results are in contrast with previous studies found no difference in NCS in diabetic patients with painful and painless DN (1,25). NCS assess large nerve fibers function while pain is mainly mediated by small myelinated (Aδ) or unmyelinated C fibers, which are invisible to NCS. Therefore, the difference between painful and painless groups in NCS in the current study is unexpected finding but could be explained by concomitant large nerve fibers involvement along with small nerve fibers in these patients. Regarding autonomic neuropathy measures, the current study showed no significant difference in DB-HRV between painful and painless DN groups. Véves et al. also reported no difference in autonomic neuropathy measures in patients with painful and painless neuropathy including DB-HRV although most of changes were in patients with severe DN in that study (21). Our findings are in contrast with another study which reported higher autonomic dysfunction in patients with painful DN and attributed this to shared small nerve fibers pathology in both sensory and autonomic nerves in patients with neuropathy (26). Neuropad staining scores, an indicator for sudomotor function, were also indifferent between painful and painless groups. We have shown in our previous study that Neuropad test is sensitive for detection of small nerve fiber neuropathy and correlates with other autonomic neuropathy tests (17). Our results indicate that autonomic neuropathy may not be involved in the genesis of DN pain.
Although several neurostructural mechanisms have been proposed for the generation of neuropathic pain in diabetes which comprise central and peripheral neural abnormalities (3), it is still unclear why some diabetic patients develop pain while the others remain free of pain and the exact underlying mechanism remains enigmatic. Apart from NCS, clinical, QST, and autonomic neuropathy assessment all did not differentiate patients with painful and painless DN in our study. Different phenotypes of DN pain have been identified where some may have deafferentation while others develop small nerve fibers hypersensitivity (2). Reduction of IENF density, length, and corneal confocal microscopy metrics have been observed in patients with painful DN as compared to painless DN groups (27) augmenting the role of small nerve fibers in the pathogenesis of DN pain. However, Sorensen et al. reported a paradoxical severe reduction in IENF in patients in those without objective signs of neuropathy as compared to painful group and concluded that various mechanisms exist for the development of DN pain (28). Higher thalamic vascularity has been also observed in type 1 diabetic patients with painful neuropathy symptoms indicating the possibility of central nervous system involvement in the genesis of DN pain (19). Increased advanced glycation end products, their receptor (RAGE) and reduced glyoxalase-I activity has been also linked to the development of DN pain (29). Indeed, the pathogenesis of DN pain is complex and even cultural and psychological factors can affect the perception of pain. Unidentified processes for DN pain makes the provision of effective treatment for this complication challenging. All the aforementioned factors could have a role for the development of pain in DN patients enrolled in the current study.

In the present study, McGill VAS scores of pain correlated significantly with cold and WT as well as DB-HRV but not with VPT or sural and peroneal nerves conduction velocities. This could be explained by the fact that VPT and NCS assess large nerve fiber function while CT, WT, and DB-HRV assess small nerve fibers, which are involved in the transmission of pain. Our findings are congruent with those of Kramer et al., who reported significant correlations between CT and WT with VAS pain scores while VPT showed no significant correlation in DN patients who were followed up for 24 months and suggested that QST could predict DN pain (4). Another study revealed correlation between CT and IENF length and that IENF length was reduced in painful DN group (27). The role of autonomic neuropathy in the development of pain is debatable as DB-HRV can be affected by stress that lead to arousal of the sympathetic system and data exploring the association between autonomic neuropathy and pain are inconsistent (26). Correlations between QST measures and DN pain indicate that QST tests can identify small nerve fibers damage and could be used for objective assessment of pain severity. Moreover, damage to these small nerve fibers could represent the early and subclinical stage of DN and consequently may facilitate detection of neural injury underlying DN pain.

Conclusion
The present work augments the notion that the development of DN pain is caused by injury to small nerve fibers with both neuronal differentiation and hyperexcitability implicated. QST is a helpful tool for identifying damage to these small fibers but cannot differentiate between painful and painless DN which suggests a generalized neural injury of NP pain. Assessment of QST, however, could be used for objective assessment of pain severity and detection of neural injury that contribute to diabetic neuropathic pain. Further large-scale studies are recommended to consolidate the evidence provided in the present study.

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Conflict of Interest
The author declares that he has no conflict of interest.

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