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Sex differences in neuropathic pain intensity in diabetes

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ABSTRACT

Introduction: Sex and gender play roles in the pain experience, such that pain is more frequent in women. Explanations for this observation range from factors related to biological sex to those related to psychosocial gender.
Objectives: To explore neuropathic pain characteristics in females with diabetes with and without established polyneuropathy.
Methods: We compared the presence and intensity of pain in males and females in 2 separate cohorts of patients with type II diabetes, with and without established diabetic polyneuropathy. Cohort #1 was recruited prospectively, while cohort #2 was studied retrospectively.
Results: Cohort #1 of 223 patients with diabetes with a relatively broad spectrum of nerve injury, showed more frequent pain in females (68% versus 53% in males), a higher frequency of additional neuropathic symptoms, and evidence of milder nerve injury. Cohort #2 of 128 patients with established diabetic polyneuropathy, showed a similar frequency of pain and additional neuropathic symptoms in both sexes. In both cohorts, females reported greater pain intensity (7.9–8.5 versus 6.8–6.9 in males, on visual analog scale).
Discussion: Though nerve injury and polyneuropathy are more common in males, females with diabetes report a higher frequency and intensity of pain despite milder polyneuropathy. Prospective epidemiological studies are required in order to confirm these findings in the community setting.

1. Introduction

Although pain affects > 25% of the world's population, it is generally more frequent in females [1], who also experience higher levels of pain [2]. Possible explanations for male and female disparities range from the biological (genetic or hormonal differences), to the psychosocial (experiential and sociocultural factors) [1]. The biological effects are often termed “sex”, and the psychosocial are called “gender” [3]. Neuropathic pain is also observed more commonly in females, and although pain in females is more likely to respond to treatment, it tends to be undertreated [4,5]. Diabetic sensorimotor polyneuropathy (DSP) constitutes the most common etiology worldwide for polyneuropathy [4,6,7], and neuropathic pain in DSP is the most prominent symptom, and is the most frequent reason for seeking medical attention [6]. Sex and gender differences in DSP have been reported, in that males have a higher frequency of DSP [8,9], but females with DSP have a higher frequency of severe neuropathic symptoms [10]. These observations suggest that sex and gender differences are relevant in both clinical and research setting.

In the current study, we aimed to explore whether neuropathic pain is more frequent and intense in females with diabetes with and without established polyneuropathy, and whether the pain is related to DSP.

2. Materials and methods

The current study included 2 separate cohorts. Cohort #1 included 251 patients with type 2 diabetes, recruited prospectively from November 2010 and May 2013, from the Diabetes and Endocrinology Clinic and the Diabetic Neuropathy Clinic at Toronto General Hospital, as part of a cross-sectional analysis of a cohort study funded by the Canadian Diabetes Association (operating grant OG-3–10–3123-BP) [9]; of these 223 had HbA1c measurements and were included in the current study. Cohort #2 was studied retrospectively and included patients with type 2 diabetes and established DSP, attending the

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Prosserman Family Neuromuscular Clinic at Toronto General Hospital, from January 2012 to December 2015. The Research Ethics Board of the University Health Network approved the current study protocol. All participants from cohort #1 signed an informed consent (prospective study). The Research Ethics Board waived informed consent for participants from cohort #2 (retrospective chart review).

All participants were ≥18 years of age and had a confirmed diagnosis of type 2 diabetes. The participants from cohort #1 were recruited irrespective of clinical or electrophysiological features indicating polyneuropathy. In contrast, participants from cohort #2 included only patients with established DSP, defined as definite polyneuropathy according to the Toronto consensus criteria [7], i.e.: based on the presence of clinical symptoms and/or signs, confirmed by abnormal objective measures, such as nerve conduction studies, or tests of small nerve fibers [11]. Patients with DSP but complicated by other potential causes of neuropathy, such as genetic, inflammatory or toxic (e.g. alcohol or chemotherapy), were excluded from the current study. Data extracted from both cohorts included demographic, clinical and electrophysiological test results, vibration perception thresholds (VPT), pain frequency and intensity as measured by the numerical rating scale (NRS), and Toronto Clinical Neuropathy Score (TCNS), including the total score, and the sub-scores for sensory symptoms, sensory deficits on exam, and reflex examination [12]. In cohort #1, small nerve fiber test results were also evaluated. As small fiber tests were not performed routinely in cohort #2, they were not studied in this cohort. In this study, we classified patients based on sex, as males or females, and did not explore gender factors. Pain intensity was measured by the NRS. Patients were asked to rate their pain level on a visual scale ranging from 0 (no pain) to 10 (worst possible pain).

The TCNS [12] is a validated scale for DSP, reflecting its severity, with a score ranging from a minimum of 0 (no neuropathy) to a maximum of 19 points. The scale combines scoring of symptoms (sensory and motor), and signs (sensory and reflex examination findings in the lower limbs). Only symptoms and signs due to DSP are scored in the TCNS.

2.1. Large nerve fiber tests

Nerve conduction studies (NCS) were performed according to the protocols of the Toronto General Hospital (University Health Network) electrophysiology laboratory, using the Sierra Wave instrument (Cadwell Laboratories Inc., Kennewick, WA, USA). Limb temperature was measured prior to nerve conduction studies, and if required, warming was performed to ensure a surface temperature of ≥32.0 °C in the hands and ≥31.0 °C in the feet. Surface stimulating and recording techniques were performed according to the standards of the Canadian Society of Clinical Neurophysiology and the American Association of Neuromuscular and Electrodiagnostic Medicine [13]. Distal latencies, amplitudes and conduction velocities were calculated automatically. Peroneal compound muscle action potential (CMAP) and sural sensory nerve action potential (SNAP) amplitudes were measured from baseline to negative peak for both, and for sensory, from positive to negative peak, if positive peak was present. Sensory and motor distal latencies were measured from onset to initial deflection from baseline. Normal values were considered as > 2 mV and > 6 μV for peroneal CMAP and sural SNAP amplitudes respectively, and as > 40 m/s for peroneal and sural nerve conduction velocities.

VPT at the fingers and toes were measured with a Neurothesiometer (Horwell Scientific, London, UK), using the method of limits [14]. Mean VPT values were calculated in volts from three separate tests, with the addition of a random “null stimulus” in order to ensure the subject's adherence and understanding. A stimulus was applied to the distal pulp of the first finger and toe on each side, with gradual increase in intensity up to a value at which the participant first detected vibration. Normal values were considered as < 5 V in the fingers, and < 15 V in the toes [8].

2.2. Small nerve fiber tests

Heat-induced axon reflex-mediated neurogenic vasodilation was measured using laser Doppler imaging (LDI). The temperature at the foot dorsum was standardized to a 32 °C using a warming blanket for at least 20 min. Subsequently, the skin above the first metatarsal head on the dorsum of the foot was heated to a temperature of 44 °C for 20 min, using a skin-heating probe (Moor Instruments Ltd., Axminster, U.K.). The MoorLDI software (version 3.11) was used in order to measure blood flow in the dermal capillaries, and the LDI flare area was calculated in centimeters squared. Normal values were > 2 cm^2, based on local laboratory normative data [11].

Cooling Detection Threshold (CDT) was tested using a method of limits with the TSA-II NeuroSensory Analyzer (Medoc Advanced Medical Systems, Ramat-Yishai, Israel). The temperature of the dorsum of the foot was gradually decreased to the first level detected by the patient as cooler than the preceding stimulus for cooling threshold testing, by using a stimulator with an initial temperature of 32 °C. After 5 repetitions, an average was calculated and compared to age-matched normative data. In addition, a catch trial with null stimulus was inserted randomly during the test [11]. Normal values were considered > 22.8 °C [9].

2.3. Statistical analysis

Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). Comparisons of demographic, clinical and electrophysiological data were made using the *t*-test, or the $\chi 2$-test, depending on whether the data was continuous or categorical. P values < .05 were considered as statistically significant.

3. Results

Cohort #1 included 223 patients with diabetes, with a relatively broad spectrum of nerve injury, including patients without DSP, and those with clinical and electrophysiological findings compatible with polyneuropathy (Tables 1 and 2). Cohort #2 included 128 patients, all with DSP (Tables 3 and 4). Within cohort #1, the females were

Table 1
Demographics, symptoms, sensory findings, and TCNS scores in 223 patients with type II diabetes (cohort #1).

	Males (n = 145)	Females (n = 78)	p-value
Age	65 ± 11	61 ± 10	**0.03**
DM duration (years)	12 ± 9	11 ± 8	0.28
HbA1c (%)	7.4 ± 1.4	7.7 ± 1.9	0.16
Symptoms			
Pain (%)	53	68	**0.03**
NRS (0–10)	6.8 ± 1.9	7.9 ± 2.1	**0.02**
Numbness (%)	64	81	**0.01**
Tingling (%)	57	72	**0.03**
Upper limb (%)	33	49	**0.02**
Weakness (%)	34	38	0.49
Ataxia (%)	41	44	0.75
Sensory deficits			
Pinprick (%)	77	75	0.84
Temperature (%)	84	78	0.25
Light touch (%)	79	74	0.37
Vibration (%)	80	65	**0.01**
TCNS scores			
Symptoms	2.8 ± 1.8	3.5 ± 1.8	**0.01**
Sensory deficits	3.5 ± 1.5	3.1 ± 1.6	0.09
Reflexes	3.6 ± 2.7	2.9 ± 2.5	0.07
Total	9.9 ± 4.4	9.5 ± 4.4	0.52

DM – Diabetes Mellitus; HbA1c – Hemoglobin A1c; TCNS – Toronto Clinical Neuropathy Score. NMR – numerical rating scale. Statistically significant p values (< 0.05) are bolded.