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Sex differences in neuropathic pain in longstanding diabetes: Results from the Canadian Study of Longevity in Type 1 Diabetes

Nancy Cardinez [a,1,2], Leif E. Lovblom [a,1], Johnny-Wei Bai [a], Evan Lewis [a], Alon Abraham [f], Daniel Scarr [a], Julie A. Lovshin [a], Yuliya Lytvyn [g], Genevieve Boulet [a], Mohammed A. Farooqi [a], Andrej Orszag [a], Alanna Weisman [a], Hillary A. Keenan [b,c], Michael H. Brent [d], Narinder Paul [e], Vera Bril [f], David Z. Cherney [g,2], Bruce A. Perkins [a,*,2]

[a] Division of Endocrinology and Metabolism, Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[b] Research Division, Joslin Diabetes Center, Boston, MA, USA
[c] Genzyme Corporation, Cambridge, MA, USA
[d] Department of Ophthalmology and Vision Sciences, Department of Medicine, University of Toronto, Ontario, Canada
[e] Joint Department of Medical Imaging, Division of Cardiothoracic Radiology, University Health Network, Toronto, Ontario, Canada
[f] Neuromuscular Diseases Unit of the Department of Neurology, Tel Aviv Sourasky Medical Center, The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[g] Division of Nephrology, Department of Medicine, University of Toronto, Ontario, Canada.

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ABSTRACT

Aim: Neuropathy and neuropathic pain are common complications of type 1 diabetes (T1D). We aimed to determine if sex-specific differences in neuropathic pain are present in adults with longstanding T1D.
Methods: Canadians with ≥50 years of T1D (n = 361) completed health history questionnaires that included assessment of neuropathy (defined by Michigan Neuropathy Screening Instrument questionnaire components ≥3; $NEUROPATHY_{MNSI-Q}$) and neuropathic pain. Multivariable logistic regression was used to determine sex-differences in neuropathic pain controlling for neuropathy.
Results: Participants had mean age 66 ± 9 years, median diabetes duration 53[51,58] years, mean HbA1c 7.5 ± 1.0%, and 207(57%) were female. Neuropathic pain was present in 128(36%) of all participants, more prevalent among those with $NEUROPATHY_{MNSI-Q}$ compared to those without [96(63%) vs. 31(15%), $p < 0.001$], and more prevalent in females compared to males [87(42%) vs. 41(27%), $p = 0.003$]. Independent of the presence of $NEUROPATHY_{MNSI-Q}$ and other factors, female sex was associated with the presence of neuropathic pain [OR 2.68 (95% CI 1.4–5.0), $p = 0.002$].
Conclusions: We demonstrated a novel sex-specific difference in neuropathic pain in females compared to males with longstanding T1D, independent of the presence of neuropathy. Further research using more objective measures of neuropathy than the MNSI is justified to further understand this sex-specific difference.
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1. Introduction

Diabetic neuropathy (DN) is a common complication of diabetes and is also frequently associated with longer duration of type 1 diabetes (T1D). Individuals with T1D are likely to experience DN and its symptomatology over their lifetime.[1] The most common form of DN is diabetic sensorimotor polyneuropathy (DSP), which affects >50% of individuals with diabetes.[2] DSP is characterized by symptoms of pain, numbness, tingling, and weakness beginning at the feet and extending proximally in a "stocking and glove" distribution. A predominant feature of DSP is neuropathic pain which affects 40–60% of individuals, and it involves "stabbing" or "burning" sensations, allodynia, aching, or hyperesthesia.[3] In due course, DN can lead to decreased quality of life, distress and depression, increased risks for ulcerations and amputations, and high healthcare costs; these sequelae have significant impact on an individual's function and care needs.[2–4] Neuropathic pain itself can have a major impact on quality of life even in the early stages of DSP.[1]

Previous adult TID and type 2 diabetes (T2D) research studies demonstrated that females experience greater neuropathic pain compared to males despite males generally having a higher prevalence and earlier age of onset of DSP.[5–8] Other research data studying familial risk factors for microvascular complications reveal the effect of sex such that if a

* Corresponding author at: Endocrinology and Metabolism, Department of Medicine, University of Toronto, Clinician Scientist, Lunenfeld-Tanenbaum Research Institute, Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, L5209-60 Murray Street Box 16, Toronto, Ontario M5T3L9, Canada.
E-mail address: bruce.perkins@sinaihealthsystem.ca. (B.A. Perkins).
[1] Indicates co-primary authors.
[2] Indicates co-senior authors.

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T1D proband is a female, the risk for developing neuropathy is 2-fold higher than the risk for a male.[9] Data from general population biochemical, clinical, genetic, and psycho-sociological research studies report greater levels of pain in females compared to males.[10] Rustoen et al. also found that in a large population study of chronic pain conditions, female participants had a higher prevalence and intensity of pain compared to males.[11] Though the cause of these sex-based differences are not explicitly known, sex-specific differences in pain may be attributed to a range of factors such as hormonal system changes, genetics, variations in the nervous system processing of pain signals, cognitive and emotional factors, behavioral coping strategies as well as sociocultural influences.[12] It is not known if increased neuropathic pain in females is related to differences in peripheral nerve dysfunction or due to differences in pain experience and reporting. A greater understanding of sex as a mediator of pain-related physiology is of significant clinical importance since the elucidation of the responsible mechanisms may improve our approach to screening and pain management.

As previous studies have documented a high prevalence of DSP in adults with longstanding TID, our aim was to determine whether there are sex-specific differences in neuropathic pain using questionnaire data from the Canadian Study of Longevity in Type 1 Diabetes cohort consisting of adults with T1D duration of ≥50 years.

2. Subjects, materials and methods

2.1. Study overview and study population

In this cross-sectional analysis we used baseline data collected from the Canadian Study of Longevity in Type 1 Diabetes (JDRF operating grant 17-2013-312), that had a primary objective to establish a registry to determine factors associated with resistance to the development of complications after longstanding T1D duration. The Canadian Study of Longevity in Type 1 Diabetes was initiated in 2013 and established a nation-wide registry of 474 people with a history of approximately 50 years or more of T1D which was confirmed through medical documentation or corroboration by a family member or friend. Of these 474 individuals invited to participate, 361 participants were eligible and completed the questionnaire (Fig. 1). Participants were contacted with the support of Diabetes Canada and JDRF Canada using public advertisements, social media, and mailings to health care professionals including primary care physicians, endocrinologists, pharmacists and from the Joslin 50-Year Medal Program which awarded medals from 1970 to individuals with >50 years of TID.[13] After establishing contact, participants were invited to participate in the first phase of the study which involved completion of a mail-based questionnaire assessing their medical and diabetes history as well as neuropathy history. All participants provided written informed consent for study participation and the study protocol was approved by the Research Ethics Board at Mount Sinai Hospital (Toronto, ON, Canada).

2.2. Data collection

Data was collected through a 35-page questionnaire that surveyed participants about their diabetes management, general medical history, history of diabetes-related complications, current medication use, demographic details, general psychological well-being, as well as recent clinical and laboratory results. Data collection was similar to previous published studies involving this cohort.[14] A combination of objective data, validated questionnaires, and self-reported outcomes were analyzed. Once participants' consents were obtained, we communicated with their healthcare providers to obtain recent measurements including blood pressure, HbA1c, lipid profile, kidney function, and funduscopic examination results. Participants were given the option to indicate their gender as male, female or prefer not to disclose; we did not explore socio-cultural factors related to gender.[15] One participant selected the option "prefer not to disclose" and their data were excluded from this current study.

2.2.1. Definition of neuropathic pain

The presence of neuropathic pain (as a binary variable) was determined from self-report of tingling/pain/burning in the extremities, allodynia or use of medications for neuropathic pain. The questionnaire items which were used to determine the presence of neuropathic pain are as follows: 1) Do you ever have any burning pain in your legs and/or feet? 2) Does it hurt when the bed covers touch your skin? 3) Do your legs hurt when you walk? 4) Have you ever experienced painful

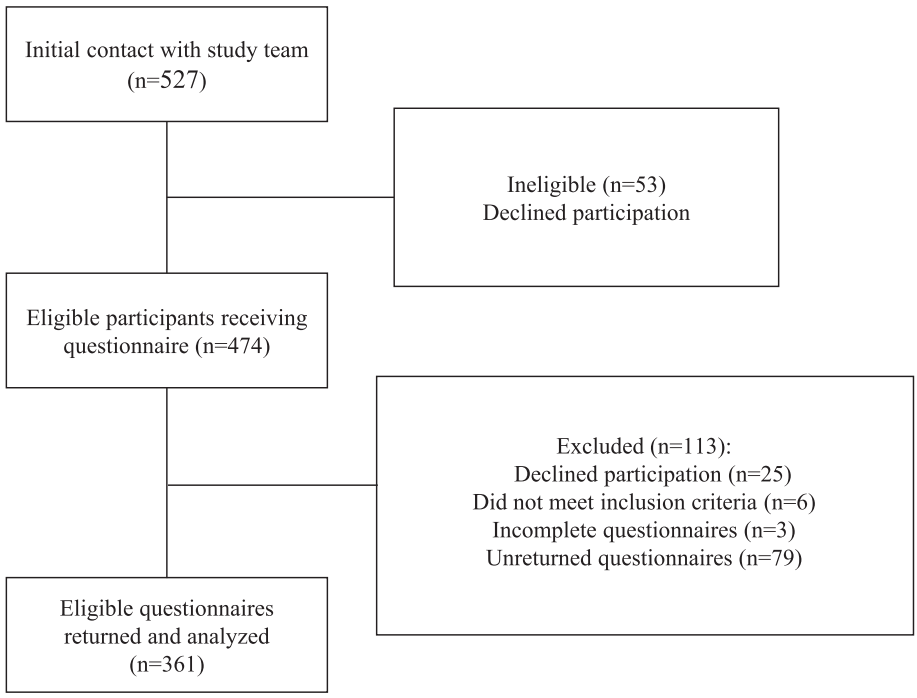

Fig. 1. Study flow diagram.

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