Diabetic Neuropathy in Hands: An Endemic Complication Waiting to Unfold?

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In this cross-sectional study we aimed to quantify the somatosensory dysfunction in the hand in people with diabetes with distal symmetrical polyneuropathy (DSPN) in hands and explore early signs of nerve dysfunction in people with diabetes without DSPN in hands. The clinical diagnosis of DSPN was confirmed with electrodiagnosis and corneal confocal microscopy. Thermal and mechanical nerve function in the hand was assessed with quantitative sensory tests. Measurements were compared between healthy participants ($n = 31$), individuals with diabetes without DSPN ($n = 35$), individuals with DSPN in feet but not hands ($DSPN_{FEET\ ONLY}$) ($n = 31$), and individuals with DSPN in hands and feet ($DSPN_{HANDS\ \&\ FEET}$) ($n = 28$) with one-way between-group ANOVA. The somatosensory profile of the hand in people with $DSPN_{HANDS\ \&\ FEET}$ showed widespread loss of thermal and mechanical detection. This profile in hands is comparable with the profile in the feet of people with DSPN in feet. Remarkably, individuals with $DSPN_{FEET\ ONLY}$ already showed a similar profile of widespread loss of nerve function in their hands. People with diabetes without DSPN in feet already had some nerve dysfunction in their hands. These findings suggest that nerve function assessment in hands should become more routine in people with diabetes.

Diabetes affects 9.3% of the global population (1) and leads to an alarming rise of complications. The most prevalent diabetes complication is neuropathy (2), which most commonly manifests as distal symmetrical polyneuropathy (DSPN). DSPN is a chronic, bilateral, length-dependent sensorimotor neuropathy characterized by an initial and progressive small-diameter nerve fiber dysfunction, followed by large-diameter myelinated nerve fiber involvement (3). Thermal deficits occur first, before loss of touch and vibration perception (4). Neuropathic pain is present in up to 26% of people with DSPN (5). Initially, the symptoms are restricted to the toes and feet, but they may gradually spread to the lower legs, fingers, and hands.

Somatosensory function in people with DSPN can be quantified with quantitative sensory testing (QST) (6). QST consists of a battery of tests to quantify loss or gain of nerve fiber function using thermal, mechanical, and electrical stimuli. DSPN is characterized by a predominant sensory hyposensitivity of small and large-diameter nerve fibers, although mechanical and thermal hyperalgesia may coexist (7). This loss of function in thermal and mechanical sensation has been well-documented for the feet in people with diabetes (8) and people with DSPN (9).

Compared with feet, DSPN in hands remains a largely understudied domain. Individuals with diabetes showed a deterioration of mechanical detection in the thumb compared with healthy participants (10), and this loss of nerve function was progressive over a 2-year period, independent of age (11). However, to date, no studies have thoroughly documented the somatosensory dysfunction of small- and large-diameter nerve fibers for the hands in people with diabetes, with or without neuropathies. Therefore, in this study we aimed to *1*) quantify

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somatosensory dysfunction in hands in people with DSPN in hands, and compare their QST profile with that of healthy people and people with diabetes without DSPN in their hands, and *2*) assess whether there are already early signs of DSPN in the hand in people with diabetes without DSPN and in people with DSPN in their feet but without neuropathy symptoms in their hands.

RESEARCH DESIGN AND METHODS

This study was part of a large research initiative (The DIAbetic NEuropathy [DIANE] Project) in which nerve function and morphology were thoroughly evaluated for better understanding of understand DSPN, with a focus on DSPN in hands.

Study Design

We conducted a cross-sectional study comparing somatosensory function in hands across four groups of participants: *1*) healthy individuals without diabetes, *2*) individuals with diabetes without DSPN, *3*) individuals with diabetes and DSPN in feet but not in hands ($DSPN_{FEET\ ONLY}$), and *4*) individuals with diabetes and DSPN in hands and feet ($DSPN_{HANDS\ \&\ FEET}$). Somatosensory function in the hands was determined via a comprehensive test battery (QST). For diagnostic and categorization purposes, clinical presentation, electrodiagnostic tests, and in vivo corneal confocal microscopy were assessed.

All participants provided written informed consent prior to participating in the study. The study was approved by the ethics committees of Griffith University (2018/669) and Queensland University of Technology (1800001224).

Participants

Participants >18 years of age with or without type 1 or 2 diabetes were eligible to participate. Participants with diabetes had to have HbA_{1c} >6.0% (42 mmol/mol), and healthy people had to have HbA_{1c} <6.0% (42 mmol/mol). Exclusion criteria were self-reported conditions that can mimic DSPN (e.g., hypothyroidism, vitamin B_{12} deficiency, degenerative disc disease, or nerve root compression), unilateral symptoms indicative of neuropathy, trauma-related nerve injuries, self-reported psychiatric disorders, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, complex regional pain syndrome, and history of malignancy/chemotherapy. People with known conditions other than diabetes that affect in vivo corneal confocal microscopy were excluded (e.g., cataract surgery in the past year, hard contact lenses, medication for glaucoma, or laser eye surgery). Participants were recruited between August 2019 and December 2020 through emails sent by Diabetes Australia and local announcements.

Group Allocation Criteria

For confirmation of the diagnosis of DSPN, participants had to meet the following two criteria: *1*) clinical presentation indicative of DSPN and *2*) confirmatory electrodiagnosis or in vivo corneal confocal microscopy. To be classified as not having DSPN, people had to not present with clinical symptoms indicative of DSPN.

Criterion 1: Clinical Presentation Indicative of DSPN

The location and type of symptoms were considered to determine whether the clinical presentation was representative of DSPN. Participants drew their symptoms on a body chart. Symptoms, such as numbness, tingling, pins and needles, and burning or aching pain, had to be bilateral and in the distal parts of the limbs. If DSPN symptoms were restricted to the lower limbs, participants with diabetes met the clinical presentation criterion for $DSPN_{FEET\ ONLY}$. If DSPN symptoms were present in lower and upper limbs, patients with diabetes met the clinical presentation criterion for $DSPN_{HANDS\ \&\ FEET}$.

Criterion 2: Electrodiagnosis

Nerve conduction is considered the gold standard for diagnosis of diabetic neuropathy. Nerve conduction tests were performed with a Sierra Summit (Cadwell, Kennwick, WA) according to recommendations from the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) project and the American Academy of Neurology (AAN) and American Association of Electrodiagnostic Medicine (AAEM) (12). Sural sensory, fibular motor, tibial motor, median sensory and motor, and ulnar motor nerves were evaluated. According to the AAN/AAEM criteria (12), an electrodiagnostic confirmation of distal symmetric polyneuropathy requires an abnormality (≥9th or ≤1st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve. However, a recent study (13) revealed better performance in using clinical criteria (i.e., the presence of various symptoms or signs), nerve conduction (i.e., fibular motor nerve conduction velocity <42 m/s), and corneal confocal microscopy (see criteria below) (13). Our primary analyses are based on these criteria (13). Additional analyses based on the AAN/AAEM criteria are described in Supplementary Material.

Criterion 3: In Vivo Corneal Confocal Microscopy

As nerve conduction can only detect abnormalities in large diameter nerve fibers, we included in vivo corneal confocal microscopy, which is an objective, rapid, noninvasive imaging technique, to identify small-diameter nerve fiber neuropathy (13). All participants underwent an examination of the subbasal nerve plexus of the cornea with the Heidelberg Retina Tomograph 3 with the Rostock Cornea Module (HRT3 RCM) (Heidelberg Engineering GmbH, Heidelberg, Germany, and Heidelberg Engineering, Smithfield, RI) according to previously published methods (14). One to eight images were manually selected for the analysis. Corneal nerve fiber length, expressed as the total length of corneal nerves in mm/mm^2, was quantified automatically with the ACCMetrics software (University of Manchester, Manchester, U.K.). The optimal threshold for confirmation of DSPN was corneal

nerve fiber length 12.5 mm/mm^2 in participants with type 1 diabetes and 12.3 mm/mm^2 in type 2 diabetes (13).

Additional Participant Characteristics

A standardized patient interview was conducted, with documentation of sex, age, BMI, ethnicity, medication use, years with diabetes, type of diabetes, diabetic neuropathy diagnosis, and years with symptoms of diabetic neuropathy. Current pain intensity and least, worst, and average pain intensity during the preceding week were measured with an 11-point numerical rating scale (NRS) (0, no pain; 10, worst pain imaginable). Blood pressure was assessed with the subject lying supine and in sitting position. HbA_{1c} level was determined with a point of care test system (Afinion Test System; Abbott, Chicago, IL).

Each participant completed a series of questionnaires. The Michigan Neuropathy Screening Instrument (MNSI) (15) was used for further description of diabetic neuropathy. It consists of 15 questions on foot sensation and pain, numbness, and temperature sensitivity. A score of $\geq$4 indicates diabetic neuropathy (15), with a higher score representing more neuropathic symptoms. We used the original questionnaire to quantify neuropathy in the feet and a modified nonvalidated version to evaluate the hands. Neuropathic pain was assessed with the DN4 questionnaire (Douleur Neuropathique en 4 Questions), which is valid for diagnosis of painful diabetic neuropathy (16). We used separate DN4 forms for feet and hands. The Brief Michigan Hand Questionnaire (BMHQ) (17) was used to evaluate hand function the ability to complete daily and occupational activities, patient satisfaction, pain, and aesthetic hand appearance. Health-related quality of life was evaluated with the five-level EQ-5D (EQ-5D-5L) questionnaire (18), with an index score based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Quantitative Sensory Testing

A comprehensive assessment of somatosensory function in the hand was performed with the standardized QST protocol described by the German Research Network on Neuropathic Pain (DFNS) (6). This battery of tests allows for quantification of loss or gain of function in small- and large-diameter nerve fibers.

With the participant blindfolded, the following tests were performed: cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensations (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), vibration detection threshold (VDT), and pressure pain threshold (PPT). All measures were performed over the thenar eminence of the dominant hand, except VDT, which was evaluated over the third metacarpophalangeal joint (MCP-III) and the ulnar styloid. PPT was also recorded at the midpoint of the upper trapezius muscle. Each test modality was measured three times and the average used in further analyses. All tests were first performed on the contralateral side to familiarize the participant with the procedures. The same instructions were given to all of the participants to control for potential bias.

As per protocol (6), all QST data except the PHS, CPT, HPT, and VDT were transformed logarithmically before statistical analysis. When pain ratings to pinprick and light touch were 0, a small constant (+0.1) was added prior to log transformation to avoid a loss of zero rating values (19). Data were converted into *z* scores (6). Positive *z* scores indicate gain of function and negative *z* scores indicate loss of function.

Thermal Detection, Thermal Pain Thresholds, and PHS

A computerized thermal stimulator (PATHWAY; Medoc, Ramat Yishai, Israel) was used for all thermal measurements. The thermode (3 × 3 cm) heated or cooled the skin at a standardized rate (1°C/s) up to safety cutoff thresholds (cold, 0°C; heat, 50°C). CDT, WDT, TSL, CPT, and HPT were measured. During the thermal detection tests, participants were asked to press a handheld switch as soon as they perceived a warmth (WDT) or cold (CDT) sensation. For TSL, participants were additionally asked to indicate the transition from alternating warmth or cold stimuli. PHS were registered during this test. For determination of pain thresholds, participants were asked to press a handheld switch as soon as the sensation of cold (CPT) or warm (HPT) became painful.

MDT

MDT were assessed with a standardized set of monofilaments (Aesthesio, DanMic Global) that exerted forces from 0.2 to 588 mN. The monofilaments were applied perpendicular to the skin for 1 s. The method of limits was used to determine five upper and five lower thresholds with application of ascending and descending stimulus intensities. The geometric mean of these five series was calculated.

Mechanical Pain Threshold

A set of seven weighted pinprick mechanical stimulators (8, 16, 32, 64, 128, 256, and 512 mN; PinPrick, MRC Systems, Heidelberg, Germany) was used. The stimulators were applied at a rate of 2 s on, 2 s off, in ascending order until the first perception of sharpness was reached. Then, the order of application was reversed until bluntness was perceived. The threshold is the geometric mean of five series of ascending and descending stimuli.

MPS and DMA

MPS was estimated with the above-mentioned weighted pinprick stimulators. DMA was estimated with light touch stimulators: a standardized brush (Somedic, Sweden) that exerted a force of 200–400 mN and a cotton wisp (3 mN) and cotton wool fixed to an elastic strip (100 mN). Participants were

asked to rate the pain produced by each of these stimuli, from 0 (no pain) to 10 (worse pain imaginable). A total of 50 stimuli (15 light touch and 35 pinprick) were delivered in five series in pseudorandom order of 10 stimuli with a time interval of 10 s between stimuli. MPS was calculated as the geometric mean of the pinprick stimuli and DMA as the geometric mean of the light touch stimulators.

VDT

A 64-Hz Rydel-Seiffer tuning fork (scale 8/8; US Neurologicals, Poulsbo, WA) was applied over the ulnar styloid and the MCP-III line. Participants needed to indicate when they could no longer feel the vibration sensation. The mean of the three measures was calculated.

PPT

An algometer (Type II; Somedic SenseLab AB, Sösdala, Sweden) with a probe area of 1 cm^2 was used to determine this threshold. Pressure was applied perpendicularly to the skin at a rate of 50 kPa/s until the participant perceived the first perception of painful pressure.

Sample Size Estimation

As in a previous study (9), the sample size was calculated on WDT (20) with use of data from similar group comparisons (8). Based on mean scores for healthy participants (1.5°C increase), diabetes without DSPN (2.1°C increase) and diabetes with DSPN (4.0°C increase) (8) and a pooled SD (3.0°C), 100 participants were needed (i.e., 25 per group) ($\alpha = 0.05$, 90% power) (G*Power 3.1.7; University of Düsseldorf, Düsseldorf, Germany). As each participant needed to attend assessments at different locations and on different days, a ∼10% dropout rate was considered. Therefore, the total required sample size was 112 participants (i.e., 28 per group).

Data Analysis

Derived from the individual body charts, summary heat maps were created with custom-written software (MathWorks, Natick, MA) for individuals with $DSPN_{FEET\ ONLY}$ and individuals with $DSPN_{HANDS\ \&\ FEET}$.

R Studio, version 3.6 (The R Foundation for Statistical Computing), was used for statistical analyses. The normality of the distribution of the data was checked with the Shapiro-Wilk test. Data were reported as mean and SD or as median with interquartile range if not normally distributed. The comparison between groups was performed with one-way ANOVA with one between-group factor with four levels. Bonferroni post hoc tests were used for pairwise comparisons when ANOVA revealed an overall significant difference between the four groups. For QST *z* scores, least significant difference post hoc tests were used in line with previous publications (9). The frequency of abnormal QST values (±1.96 SD from healthy control subjects) was quantified as loss or gain of function. Fisher exact tests with pairwise comparisons were used to compare differences in frequencies between groups. The level of significance was $P < 0.05$. Consistent with recommendations (21), the influence of age and sex on QST variables was explored with ANCOVA. Because both factors were not significant, *z* scores were not adjusted for age or sex.

RESULTS

Participants and Groups

A total of 660 individuals with and without diabetes were screened over the phone. Of these, 147 were selected for face-to-face screening; 125 met the selection criteria and were allocated to the following groups: *1*) healthy participants, $n = 31$; *2*) diabetes without DSPN, $n = 35$; *3*) diabetes with $DSPN_{FEET\ ONLY}$, $n = 31$; and *4*) diabetes with $DSPN_{HANDS\ \&\ FEET}$, $n = 28$ (Supplementary Fig. 1).

Additional Participant Characteristics

Demographic characteristics and medication use are summarized per group in Table 1 and Supplementary Table 1. Supplementary Table 2 provides an overview of the electrodiagnostic and corneal confocal microscopy results used for group classification. The heat maps (Fig. 1) revealed that people with $DSPN_{HANDS\ \&\ FEET}$ also had more widespread DSPN symptoms in their lower legs.

Regarding questionnaires, people with $DSPN_{HANDS\ \&\ FEET}$ had worse hand function (BMHQ) and poorer quality of life (EQ-5D-5L) compared with all other groups (Table 1). Mobility, activities, self-care, and pain/discomfort of the EQ-5D-5L decreased across the groups (healthy, diabetes without neuropathy, $DSPN_{FEET\ ONLY}$, and $DSPN_{HANDS\ \&\ FEET}$) (Supplementary Fig. 2). Individuals with $DSPN_{HANDS\ \&\ FEET}$ scored higher in presence of neuropathic symptoms (MNSI) and neuropathic pain (DN4) than individuals with $DSPN_{FEET\ ONLY}$.

Quantitative Sensory Testing

All participants completed the QST protocol, and there were no missing data.

Somatosensory Profile of Individuals With DSPN in Hands

The somatosensory profile of hands in individuals with $DSPN_{HANDS\ \&\ FEET}$ was predominantly characterized by poorer thermal detection threshold and MDT (Fig. 2*A* and *B* and Supplementary Table 3). For seven of the 14 QST variables (CDT, WDT, TSL, HPT, MDT, PPT [trapezius], and VDT [MCP-III], individuals with $DSPN_{HANDS\ \&\ FEET}$ had worse somatosensory function in their hands compared with healthy participants (all $P \leq 0.013$) and compared with individuals with diabetes without DSPN (all $P \leq 0.016$). Interestingly, apart from CDT ($P < 0.0046$), there were no significant differences in somatosensory profile in the hand between individuals with $DSPN_{HANDS\ \&\ FEET}$ and individuals with $DSPN_{FEET\ ONLY}$, indicating that individuals with $DSPN_{FEET\ ONLY}$ already have small- and large-diameter nerve fiber dysfunction in their hands.

Table 1—Overview of demographic characteristics

	Healthy participants (n = 31)	Diabetes without DSPN (n = 35)	$DSPN_{FEET\ ONLY}$ (n = 31)	$DSPN_{HANDS\ \&\ FEET}$ (n = 28)	ANOVA results	Pairwise differences
Age, years	50.0 (24.7)	47.3 (17.0)	58.6 (12.5)	60.1 (9.1)	0.001	2–3,* 2–4**
Female, n (%)	18 (58)	15 (43)	8 (35)	13 (46)	0.081	
BMI, kg/m^2	24.3 (4.3)	27.6 (5.1)	32.5 (7.1)	32.4 (8.3)	<0.001	1–3,*** 1–4,*** 2–3,* 2–4*
Ethnicity, n (%)						
Asian	4 (12)	8 (23)	0 (0)	1 (4)		
Indigenous Australian	0 (0)	0 (0)	1 (3)	2 (7)		
Mixed	1 (3)	2 (6)	1 (3)	1 (4)		
White	26 (84)	23 (66)	27 (87)	24 (86)		
Not reported	0 (0)	3 (9)	2 (7)	0 (0)		
Type 2 diabetes	0 (0)	17 (49)	21 (68)	24 (86)	0.016	
Pain intensity (NRS 0–10)						
Least pain last week	0.4 (0.8)	0.5 (1.1)	1.2 (1.4)	2.4 (2.2)	<0.001	1–4,*** 2–4,*** 3–4**
Worst pain last week	1.8 (2.1)	1.7 (1.8)	3.4 (2.9)	5.2 (2.6)	<0.001	1–4,*** 2–3,* 2–4,*** 3–4*
Average pain last week	1.0 (1.3)	1.1 (1.4)	2.4 (2.2)	4.0 (2.4)	<0.001	1–3,* 1–4,*** 2–3,* 2–4,*** 3–4**
Pain at the moment	0.3 (0.9)	1.2 (1.7)	1.5 (2.1)	3.3 (2.4)	<0.001	1–4,*** 2–4,** 3–4*
Years with diabetes	—	12.5 (10)	15.5 (10.2)	11.8 (8.3)	0.87	
Years with DSPN	—	—	3.6 (4.3)	4.8 (5.4)	0.35	
HbA_{1c}, %	5.4 (0.3)	6.6 (0.8)	7.7 (1.2)	8.2 (2.0)	<0.001	1–2,* 1–3,*** 1–4,*** 2–4**
HbA_{1c}, mmol/mol	36 (3.3)	49 (8.7)	61 (13.1)	66 (21.9)		
Awareness of DSPN (yes)	—	—	18 (58)	17 (61)	1	
SBP/DBP (supine), mmHg	119.9 (16.6)/ 72.2 (7.8)	122.6 (13.5)/ 75.7 (8.3)	136.6 (24.2)/ 81.1 (14.3)	133.8 (17.1)/ 81.1 (8.8)	0.0012	1–3,** 2–3*
SBP/DBP (standing), mmHg	125.1 (15.4)/ 78.2 (7.1)	124.0 (15.0)/ 80.6 (7.1)	135 (19.4)/ 81.1 (10.3)	136.6 (33.2)/ 82.5 (8.6)	0.0096	
Questionnaires						
MNSI feet	1.2 (1.1)	1.8 (1.5)	5.2 (2.7)	6.9 (2.5)	<0.001	1–3,*** 1–4,*** 2–3,*** 2–4,*** 3–4**
MNSI, hands	0.5 (0.8)	0.9 (0.9)	1.5 (1.6)	3.6 (1.7)	<0.001	1–3,** 1–4,*** 2–4,*** 3–4***
DN4, feet	0.2 (0.5)	0.4 (0.6)	4.0 (2.2)	5.5 (1.8)	<0.001	1–2,*** 1–3,*** 1–4,*** 2–3,*** 2–4,*** 3–4***
DN4, hands	0.1 (0.3)	0.2 (0.6)	0.9 (1.7)	3.0 (1.6)	<0.001	1–3,** 1–4,*** 2–4,*** 3–4***
BMHQ	96.3 (7.6)	93.5 (7.5)	90.3 (12.4)	76.5 (16.7)	<0.001	1–4,*** 2–4,*** 3–4***
EQ-5D-5L	1 (0.1)	0.9 (0.1)	0.9 (0.1)	0.8 (0.2)	<0.001	1–3,* 1–4,*** 2–4,*** 3–4*

Data presented as means (SD) appear with pairwise differences (one-way ANOVA and Bonferroni post hoc tests), where pairwise differences indicate significant P values between group pairs: 1, healthy participants; 2, diabetes without DSPN; 3, $DSPN_{FEET\ ONLY}$; 4, $DSPN_{HANDS\ \&\ FEET}$. Categorical data were analyzed with the χ^2 test and are presented as reported values (percentages). DBP, diastolic blood pressure; SBP, systolic blood pressure. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

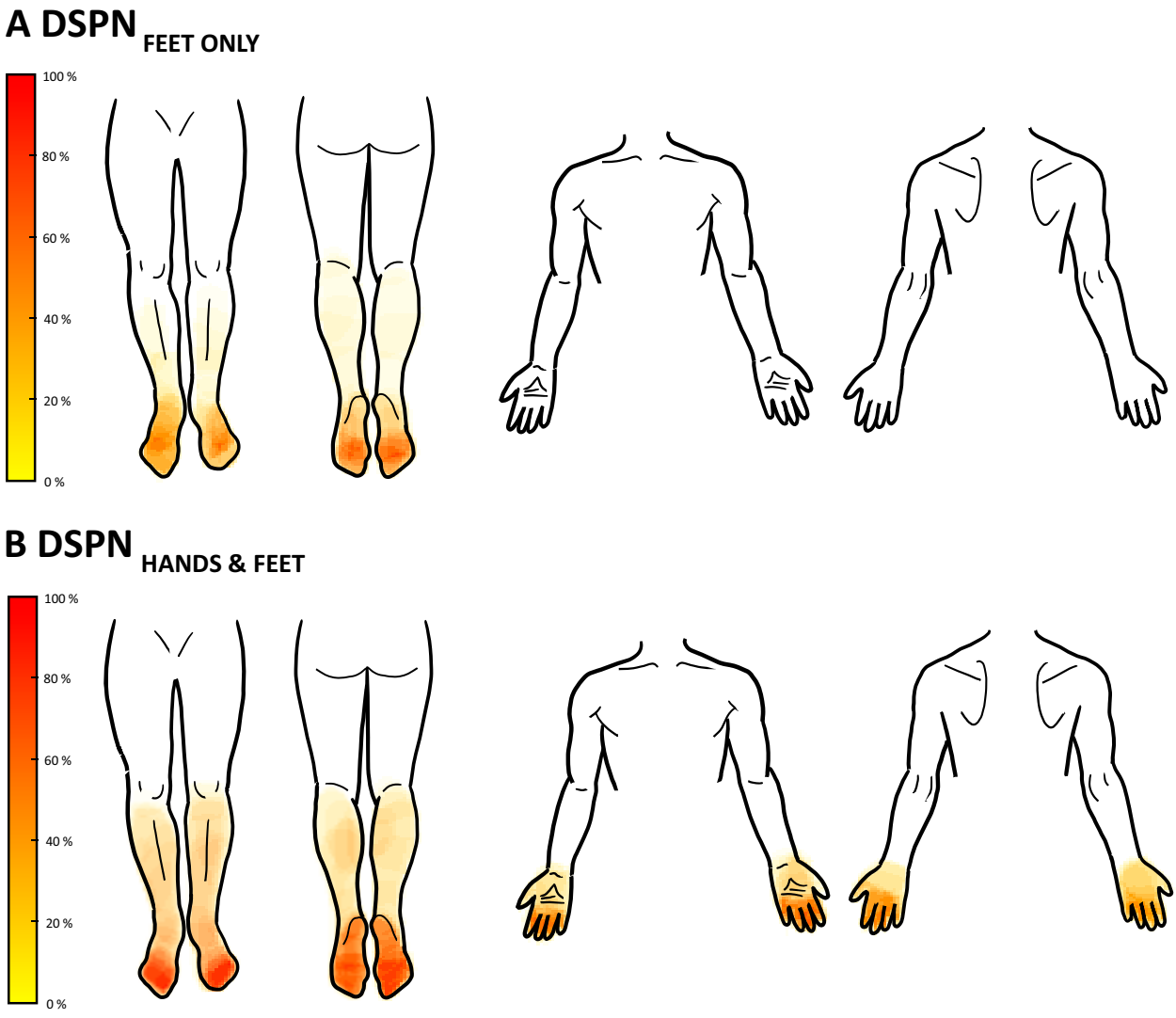

Figure 1—Heat maps of the location of symptoms in individuals with DSPN in feet only (*A*) and individuals with DSPN in hands and feet (*B*). The heat bar represents the percentage of participants in each group.

The findings of a somatosensory profile of DSPN in hands predominantly characterized by loss of nerve fiber function were confirmed when only individuals with abnormal values were considered (i.e., scores outside the normal ranges) (Fig. 3). A larger percentage of individuals with $DSPN_{HANDS\ \&\ FEET}$ showed loss of thermal, mechanical, and vibration detection compared with healthy participants (CDT 39% vs. 3%, WDT 36% vs. 3%, TSL 50% vs. 0%, MDT 71% vs. 6%, and VDT [MCP-III] 46% vs. 0%, respectively; all $P \leq 0.0018$). Loss of function was observed for PHS (23% vs. 0%; $P = 0.0035$).

Early Signs of DSPN in Hands in Individuals With DSPN in Feet

Individuals with $DSPN_{FEET\ ONLY}$ already had nerve dysfunction in their hands, which was further evidenced in comparisons of their somatosensory profile with the profiles of healthy individuals or individuals with diabetes without DSPN. For 7 of the 14 QST variables obtained (WDT, TSL, HPT, MDT, PPT [trapezius], VDT [MCP-III and ulna]), individuals with $DSPN_{FEET\ ONLY}$ showed worse somatosensory function compared with that of individuals with diabetes without DSPN ($P \leq 0.035$). Apart from PPT (trapezius), these variables were also worse for individuals with $DSPN_{FEET\ ONLY}$ compared with healthy participants ($P \leq 0.024$) (Fig. 2*A* and *B* and Supplementary Table 3).

When only individuals with values outside the normal ranges were considered (Fig. 3), a larger percentage of individuals with $DSPN_{FEET\ ONLY}$ showed loss of function in TSL, MDT, and VDT (MCP-III)) compared with individuals with diabetes without DSPN (all $P \leq 0.001$) and, additionally, in VDT (ulna) compared with healthy

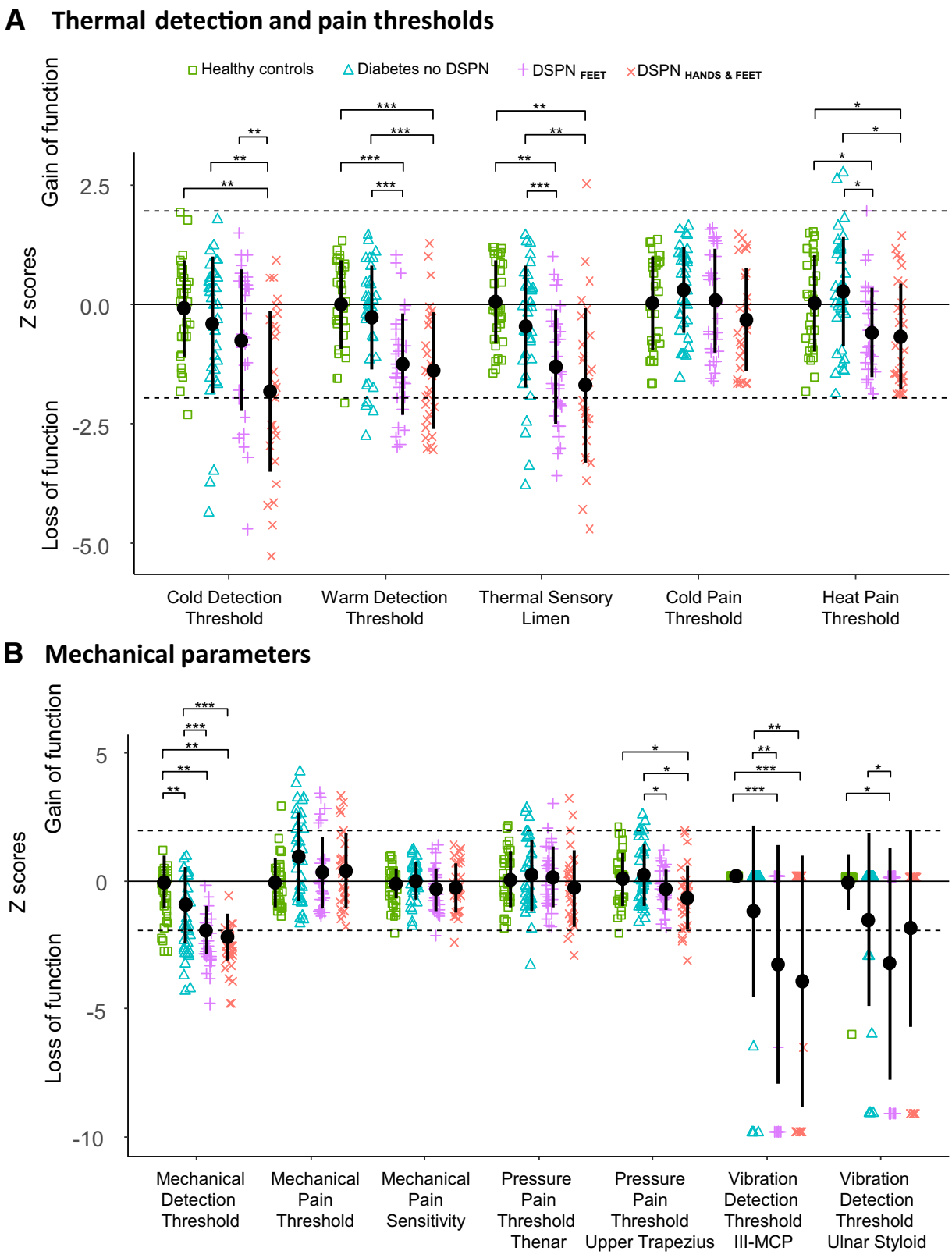

Figure 2—Scatterplot and mean (95% CI) of *z* scores for thermal detection and pain thresholds (*A*) and mechanical parameters (*B*) in healthy participants, people with diabetes without DSPN, people with $DSPN_{FEET\ ONLY}$, and people with $DSPN_{HANDS\ \&\ FEET}$. Results of the one-way ANOVA, least significant difference post hoc test are indicated as follows: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. Dotted lines indicate upper and lower limits for 95% CI of the distribution of healthy participants. Note that most participants reached the safety cutoff temperature for CPT.

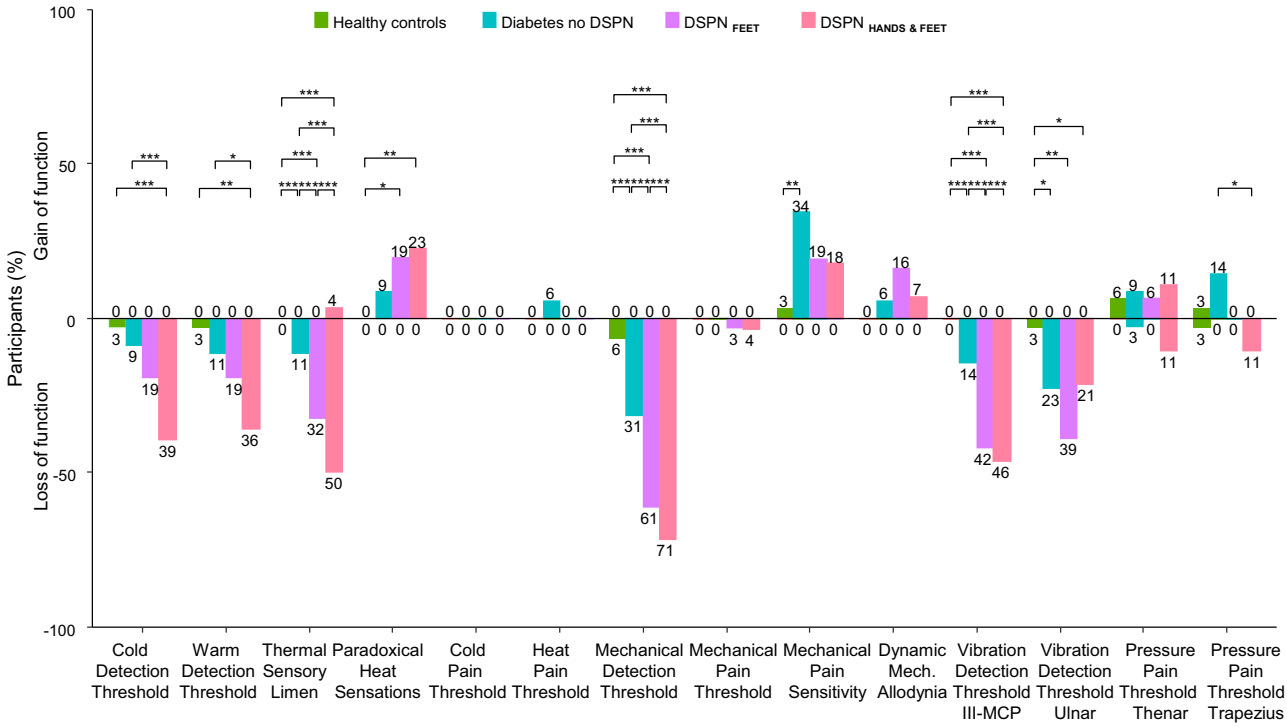

Figure 3—Frequencies and comparison of abnormal QST values (±1.96 SD from mean values from healthy group) for healthy participants, people with diabetes without DSPN, people with $DSPN_{FEET\ ONLY}$, and people with $DSPN_{HANDS\ \&\ FEET}$. Fisher exact test, post hoc comparison: *P <0.05; **P < 0.01; ***P < 0.001. Mech., mechanical.

participants (all $P < 0.0011$). Loss of function was observed for PHS compared with healthy participants ($P = 0.024$).

Early Signs of DSPN in Hands in Individuals With Diabetes Without DSPN

Individuals with diabetes without DSPN showed a loss of somatosensory function in the hands compared with healthy participants for MDT ($P < 0.002$) (Fig. 2*B*). When only abnormal findings were considered, loss of function was observed in TSL, MDT, and VDT (MCP-III and ulna) in individuals with diabetes without DSPN compared with healthy participants (all $P < 0.030$). Gain of function was observed for MPS ($P = 0.0016$) (Fig. 3).

Sensitivity Analyses

The comparison between groups based on the AAN/AAM criteria revealed the same findings (Supplementary Table 4). Similarly, excluding participants who might have had bilateral CTS rather than DSPN in hands did not change our findings (Supplementary Table 5).

DISCUSSION

The first aim of this study was to quantify the somatosensory dysfunction in hands in people with DSPN in hands. The somatosensory profile was predominantly characterized by loss of nerve fiber function in small- and large-diameter nerve fibers and manifested itself as widespread loss of thermal and mechanical detection. Gain of nerve fiber function was restricted to increased pain sensation in response to some mechanical but not thermal stimuli. Overall, this somatosensory profile is comparable with the profile identified in feet in individuals with DSPN in feet (20).

The second aim was to assess whether there were early signs of nerve dysfunction in the hand that could be detected in individuals with diabetes without DSPN and individuals with $DSPN_{FEET\ ONLY}$ (i.e., preclinical signs of DSPN in hands). Clear signs of somatosensory dysfunction were present in individuals with $DSPN_{FEET\ ONLY}$. Moreover, the somatosensory dysfunction in individuals with $DSPN_{FEET\ ONLY}$ was comparable with that in individuals with $DSPN_{HANDS\ \&\ FEET}$. To a lesser extent, individuals with diabetes without DSPN already showed signs of nerve fiber dysfunction in their hands.

We believe that the main findings of this study (i.e., widespread loss of small- and large-diameter nerve fiber function in the hand in individuals with DSPN in hands and the early signs of nerve fiber dysfunction in the hand in individuals with diabetes without symptoms of DSPN in hands) are important. The development of diabetes at a younger age is associated with more severe complications, including DSPN (22). Already ∼50% of patients with diabetes develop DSPN in their feet within their lifetime (23). As DSPN in hands is a progression from DSPN in feet and due to an earlier onset of diabetes in life, the

prevalence of DSPN in hands is likely to increase substantially over time. DSPN in hands may become an endemic complication of diabetes if no action is taken.

A rise in DSPN in hands would be worrisome, as the somatosensory pattern of widespread small- and large-diameter nerve fiber dysfunction is similar for hands (in people with DSPN in hands) and feet (in people with DSPN in feet). Our findings show that people with DSPN in hands have poorer hand function and quality of life. Risk factors, such as elevated levels of hyperglycemia (24), hypertension (25), and obesity (26), were prevalent in people with $DSPN_{HANDS\ \&\ FEET}$ and $DSPN_{FEET\ ONLY}$. Yet, people with $DSPN_{HANDS\ \&\ FEET}$ experienced more intense pain as reflected by the NRS scores and DN4 questionnaires. The higher pain levels for those with $DSPN_{HANDS\ \&\ FEET}$ may have contributed to poorer hand function (9,27) and quality of life (28).

Whereas DSPN in feet contributes substantially to disability and health care costs (29), including foot ulceration and amputation (30), the impact of DSPN in hands has not yet been explored. Although a troubling new entity (31), hand ulcers are likely to remain less prevalent than foot ulcers (32). Yet, the impact of DSPN in hands should not be underestimated. The hand has a specialized role in tactile perception (33–36). The somatosensory dysfunction in hands observed in this study affects dexterity (37), which is important for optimal hand function, including evaluating glycemic levels in the self-management of diabetes (27). This may hamper glycemic control and exacerbate DSPN (9,38). Modification of risk factors, such as hyperglycemia (24), hypertension (25), and obesity (26), may prevent the development and progression in people with painless DSPN (39,40) and, with less certainty, in people with painful DSPN (41).

Carpal tunnel syndrome (CTS), a compressive mononeuropathy affecting the median nerve at the wrist, can be present in up to 22.4% of people with DSPN (42). The diagnosis of CTS in underlying DSPN is challenging because DSPN can obscure the electrophysiological findings of CTS, especially in advanced DSPN (42). Possibly, some individuals in the $DSPN_{HANDS\ \&\ FEET}$ group might have had DSPN in feet with bilateral CTS rather than DSPN in hands and feet. However, a sensitivity analysis revealed that exclusion of these few patients did not alter our findings. In this exploratory study, we decided to include people with type 1 and type 2 diabetes. Considering different pathophysiological mechanisms (43), further research is needed for investigation of whether the reported observations are equally present for type 1 as type 2. Finally, individuals with $DSPN_{HANDS\ \&\ FEET}$ reported more intense pain than individuals with $DSPN_{FEET\ ONLY}$, which may contribute to some of the differences that we observed between these two groups.

Based on the findings of this study, we advocate for an increased awareness of DSPN in hands among people with diabetes, clinicians, and researchers. This study may initiate a discussion on more routine assessment of hands in people with diabetes.

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