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Sensory Phenotypes Provide Insight Into the Natural Course of Diabetic Polyneuropathy

Dimitrios Tsilingiris, Lukas Schimpfle, Ekaterina von Rauchhaupt, Alba Sulaj, Lukas Seebauer, Stephan Herzig, Julia Szendroedi, Stefan Kopf, and Zoltan Kender

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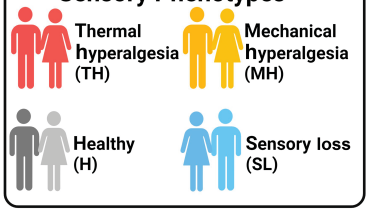
Common Pathway to Sensory Loss in Patients With Diabetes

Aim/Method

Characterization of lower-extremity sensory subphenotypes in patients with diabetes

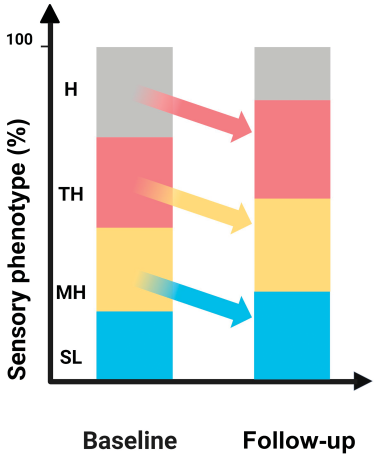
Q uantative
S ensory
T esting

Sensory Phenotypes

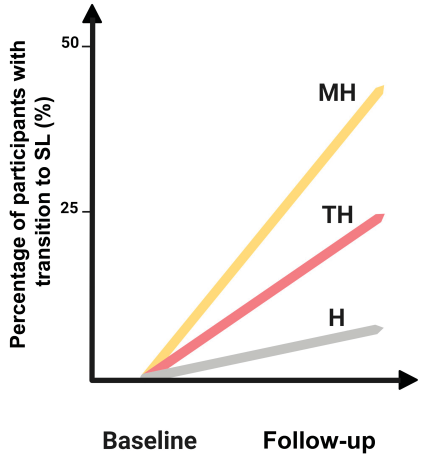


Results

Change in sensory phenotypes over time

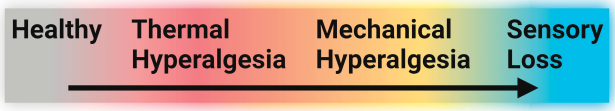


Occurrence of SL after baseline visit with respect to initial sensory phenotype



Conclusion

Thermal and mechanical hyperalgesias are potential consecutive tranisitonal phenotypes in the development of sensory loss in diabetic neuropathy.



Sensory Phenotypes Provide Insight Into the Natural Course of Diabetic Polyneuropathy

Dimitrios Tsilingiris,[1,2] Lukas Schimpfle,[1] Ekaterina von Rauchhaupt,[1,2] Alba Sulaj,[1,2] Lukas Seebauer,[1] Stephan Herzig,[2,3,4] Julia Szendroedi,[1,2,3] Stefan Kopf,[1,2] and Zoltan Kender[1,2]

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We aimed to investigate the characteristics and longitudinal course of sensory phenotypes identified through quantitative sensory testing (QST) in the frame of diabetic sensorimotor polyneuropathy (DSPN). A total of 316 individuals with diabetes were examined (type 2 diabetes 78.8%), 250 of whom were undergoing follow-up visits at 1, 2, and/or 4 (2.88 ± 1.27) years. Allocation into four sensory phenotypes (healthy, thermal hyperalgesia [TH], mechanical hyperalgesia [MH], and sensory loss [SL]) at every time point was based on QST profiles of the right foot. Cross-sectional analysis demonstrated a gradual worsening of clinical and electrophysiological sensory findings and increased DSPN prevalence across the groups, culminating in SL. Motor nerve impairment was observed solely in the SL group. Longitudinal analysis revealed a distinct pattern in the developmental course of the phenotype (from healthy to TH, MH, and finally SL). Those with baseline MH exhibited the highest risk of transition to SL. Reversion to healthy status was uncommon and mostly observed in the TH group. Among those without DSPN initially, presence or future occurrence of SL was associated with a three- to fivefold higher likelihood of DSPN development. Our comprehensive longitudinal study of phenotyped patients with diabetes elucidates the natural course of DSPN. QST-based sensory examination together with other tools for phenotyping may be useful in determining the natural course of diabetic neuropathy to identify patients at high risk of DSPN and guide preventive and therapeutic interventions.

ARTICLE HIGHLIGHTS

- The course of diabetic sensorimotor polyneuropathy (DSPN) development, from healthy status to overt DSPN, is poorly understood.
- We studied the characteristics and longitudinal appearance of lower-extremity sensory phenotypes (healthy, thermal hyperalgesia [TH], mechanical hyperalgesia [MH], and sensory loss [SL]) identified through quantitative sensory testing in individuals with diabetes.
- There was an increasing severity and patterned order of longitudinal appearance across healthy, TH, MH, and SL phenotypes. SL was most strongly associated with formal DSPN.
- Our findings provide insight into the natural history of DSPN. Sensory phenotyping can be implemented to identify high-risk individuals and those most likely to benefit from therapeutic interventions.

It is estimated that approximately half of patients with diabetes will be affected by diabetic sensorimotor polyneuropathy (DSPN) during their lifetimes. DSPN and related complications substantially contribute to diabetes-related morbidity and health care costs (1). The underlying pathogenesis of DSPN remains unclear; therefore, the development of comprehensive strategies to prevent the onset and progression of DSPN is a major challenge.

In the context of DSPN progression, it has been suggested that small fiber dysfunction and/or loss precedes large fiber impairment in DSPN (2,3). Furthermore, peripheral sensory dysfunction antecedes motor impairment, which is perceived

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to occur in late stages in the course of DSPN development (4). Therefore, the focus has been on the optimal method of small fiber assessment for early DSPN screening (5,6). As an additional tool for invasive laborious methods, such as intraepidermal nerve fiber density (IENFD) and corneal confocal microscopy, quantitative sensory testing (QST) has been suggested as a low-cost and time-efficient noninvasive method to assess small fiber dysfunction and has had a substantial impact in clinical studies (5–7).

The 13 QST domains of the protocol of the German Research Network on Neuropathic Pain (DFNS) offer an assessment of both small and large fibers as well as recognition of states associated with gain (hyperalgesia and allodynia) or loss (hypoalgesia and hypoesthesia) of sensory function (7). Moreover, the DFNS protocol allows for clustering of patients with peripheral neuropathy into distinct sensory phenotypes, which are likely related to different underlying pathophysiological mechanisms (8–10). Previous reports have described sensory loss (SL) as the most commonly encountered phenotype in DSPN, followed by mechanical hyperalgesia (MH) and thermal hyperalgesia (TH) (8,11). However, electrophysiological assessment combined with prospective longitudinal analysis of these phenotypes of DSPN has not yet been performed. The phenotypes determined by QST have also been replicated among healthy individuals using surrogate pain models (10). Therefore, QST is also applicable in preclinical states of DSPN and might thus map the progression from early states of the disease toward the full-blown clinical condition. Although QST was originally established in states of painful peripheral neuropathy from various etiologies (8,9), recent studies have demonstrated overlapping phenotypic prevalences in painful and painless conditions (11,12). Furthermore, sorting algorithms allow the distinction between a sensory healthy state and each of the neuropathic phenotypes (TH, MH, and SL) (9). According to the deterministic version of the algorithm, each patient is assigned to the unique phenotype category to which the QST profile is most similar (9).

In the current study, we aimed to comparatively investigate the general and neurological features of the four sensory phenotypes identified through QST (healthy, TH, MH, and SL) in patients with type 1 diabetes (T1D) or type 2 diabetes (T2D) across a spectrum of peripheral neural status, ranging from absence of sensory abnormalities to established DSPN. Furthermore, we examined the evolution of sensory phenotypes over an average timespan of ∼3 years in order to offer a comprehensive evaluation of the natural history of DSPN development.

RESEARCH DESIGN AND METHODS

Study Sample

This was an analysis of data from the Heidelberg Study of Diabetes and Complications (HEIST-DiC). The study was conducted according to the principles of the Declaration of Helsinki, and all participants provided written informed consent before their inclusion. The study protocol has been approved by the ethics committee of Heidelberg University Hospital (Heidelberg, Germany).

All participants in the HEIST-DiC study with either T1D or T2D and a full set of available baseline data (n = 316) and at least one follow-up visit (n = 250) were included in the cross-sectional and longitudinal analyses, respectively.

The study protocol has been previously described (13,14). All investigations took place during morning visits. Medical history, including current medication, was obtained using standardized questionnaires.

HbA_{1c} was measured on a BIORAD (Hercules, CA) Variant II analyzer (coefficient of variation 5.2%).

Peripheral Neurological Examinations

Underlying causes of peripheral neuropathy other than diabetes (e.g., advanced renal disease stage, B12 deficiency, alcohol consumption >14 units per week, and unregulated thyroid disorders) were excluded before further testing. Apart from QST (see below), all participants underwent neuropathic symptom evaluation and clinical examination. The neuropathy symptom (NSS) and disability scores (NDS) were used to assess the extent of neuropathic subjective symptoms and objective findings. Electrophysiological testing was carried out on a Viking IV electromyography device (Nicolet, Middleton, WI). Right lower-extremity nerve conduction velocity (NCV), sensory nerve action potential (SNAP; sural), and composite motor action potential (CMAP; common peroneal and tibial) were registered. In the case of nondetectable SNAP/CMAP, values below the first percentile were assumed, and for comparisons of continuous NCV/SNAP/CMAP between groups, data were imputed with the lowest measurable values in our cohort. As an additional sensitivity analysis, comparisons were repeated after imputing the lowest measurable values by 2 and after converting the continuous values into binary variables (normal/pathological) using the 2.5th percentile as the cutoff, which yielded identical results.

DSPN Definitions

Diagnosis of DSPN was made *1*) on the basis of clinical criteria, defined as the presence of either at least moderate neuropathic deficits (NDS ≥6) or the combination of mild deficits with moderate neuropathic symptoms (NSS ≥5 together with NDS 3–5) (15), or *2*) according to the Toronto consensus definition of confirmed DSPN, defined as the presence of sural SNAP or NCV below the first percentile, together with at least one motor nerve abnormality, and presence of symptoms and/or signs of DSPN (NDS and/or NSS ≥3) (16).

QST and Sensory Phenotyping

The allocation of patients into the TH, MH, or SL phenotype or healthy state category was made via the deterministic algorithm proposed by Vollert et al. (9) using the 13 domains of QST. In the context of the current article, the term healthy denotes the absence of sensory abnormalities

falling into the categories of TH, MH, and SL and does not concern a patient's overall health status. Patients receiving pain medication were asked to refrain from taking opioids for at least 24 h and other analgesics for at least 48 h before testing. In short, all 13 QST parameters (cold detection threshold, warm detection threshold, perception of alternating warm and cold stimuli, paradoxical heat sensation, cold pain threshold, heat pain threshold, mechanical detection threshold, vibration detection threshold, pinprick pain threshold, blunt pressure pain threshold, stimulus/response functions for pinprick sensitivity, dynamic mechanical allodynia [DMA], and pain summation to repetitive pinprick stimuli [known as the wind-up ratio]) were measured on the right foot of each participant according to the standardized protocol of the DFNS (17). The corresponding age- and sex-matched *z* scores for this anatomical area were obtained. The presence or absence of paradoxical heat sensation was coded as a binary variable with value 2 or 0, respectively. Absence of DMA and DMA with average pain ratings 0 to 1 and 1 to 100 were coded as 0, 2, and 3, respectively. The personnel performing the QST were blinded to the potential past QST values and profiles of each examined patient. According to the deterministic algorithm, the probability of the presence of each of the four phenotypes was calculated based on the 13-item QST profile, and the phenotype with the greatest probability was assigned to each participant at each time point (9). The data presented here from the classification into sensory phenotypes were generated for all participants, for all available follow-up time points, at the same time by applying the published formulas for our whole data set.

Statistical Analysis

Statistical analysis was carried out using the IBM SPSS statistical package (version 25.0) and GraphPad Prism (version 9.4.1). Values are presented as mean ± SD or median (25th, 75th interquartile range) for qualitative and *n* (%) for qualitative variables. For comparisons of quantitative variables across the four sensory phenotypic groups, depending on the normality of their distribution, one-way ANOVA or the Kruskall-Wallis test was used, whereas those for quantitative data were carried out using the χ^2 test. In case of statistically significant differences ($P < 0.05$), post hoc pairwise group comparisons with Bonferroni correction were performed. Where needed, ANCOVA was used to adjust the means for potential confounding factors. For cross-sectional analysis of binary outcomes, univariable and multivariable logistic regressions were conducted, and the odds ratios (ORs) with 95% CIs are reported.

To investigate the patterns of longitudinal transition of each baseline sensory phenotype, a one-sample χ^2 test for goodness of fit was conducted using the frequencies of the phenotypes of change, with post hoc pairwise tests when statistically significant deviations from expected frequencies were noted. For the prospective analysis of binary outcomes (occurrence of specific sensory phenotype or DSPN) in the course of follow-up, Cox proportional hazards regression models were used. The unadjusted crude hazard ratios (HRs) with 95% CIs are reported, along with HRs after adjustment (aHRs) for age, sex, diabetes type, diabetes duration, BMI, waist-to-hip ratio, HbA_{1c}, estimated glomerular filtration rate (eGFR), cholesterol, known cardiovascular disease, use of cholesterol-lowering drugs, and analgesic therapy (anticonvulsants, serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, and opioids). *P* values <5% were considered statistically significant.

Data and Resource Availability

The data sets generated and/or analyzed during the current study are available from the corresponding authors upon reasonable request. No applicable resources were generated or analyzed during the current study.

RESULTS

On the basis of their QST profiles, of the originally 316 examined participants, 80 (25.3), 91 (28.8), 77 (24.4), and 68 (21.5) were classified as healthy or as belonging to TH, MH, and SL groups, respectively using the deterministic sorting algorithm (Fig. 1). A comparative presentation of group characteristics is provided in Table 1.

Baseline Group Comparison

Main Baseline Characteristics

Mean age differed significantly across the groups, with participants in all neuropathic phenotypes exhibiting significantly older age than the healthy group. eGFR also differed, with mean eGFR values remaining within or close to the normal range in all subgroups; however, this difference was abolished after adjustment for age (ANCOVA $P = 0.133$). The four subgroups were similar regarding sex and diabetes type as well as BMI and diabetes duration. Cholesterol concentration was lower in the neuropathic groups compared with the healthy group, with opposite trends as regards the frequency of cholesterol-lowering medication use.

Neurological Assessment and Prevalence of DSPN

Peripheral neurological findings were consistent with a gradually increasing severity of neuropathic findings across healthy, TH, MH, and SL groups, respectively (Table 1 and Fig. 2). Clinical objective findings worsened across the groups as indexed by higher NDS values, which were higher in TH and MH groups than in the healthy group and higher in the SL group than in all other groups. The extent of neuropathic symptoms (NSS) was greatest in MH and SL groups, which were comparable to each other, whereas neuropathic symptoms were virtually absent in healthy and TH groups. Sural NCV was lowest in the SL group, whereas interestingly, SNAP, which reflects fiber density, was similar in healthy and TH groups and lowest in MH and SL groups. Neurophysiological findings of common

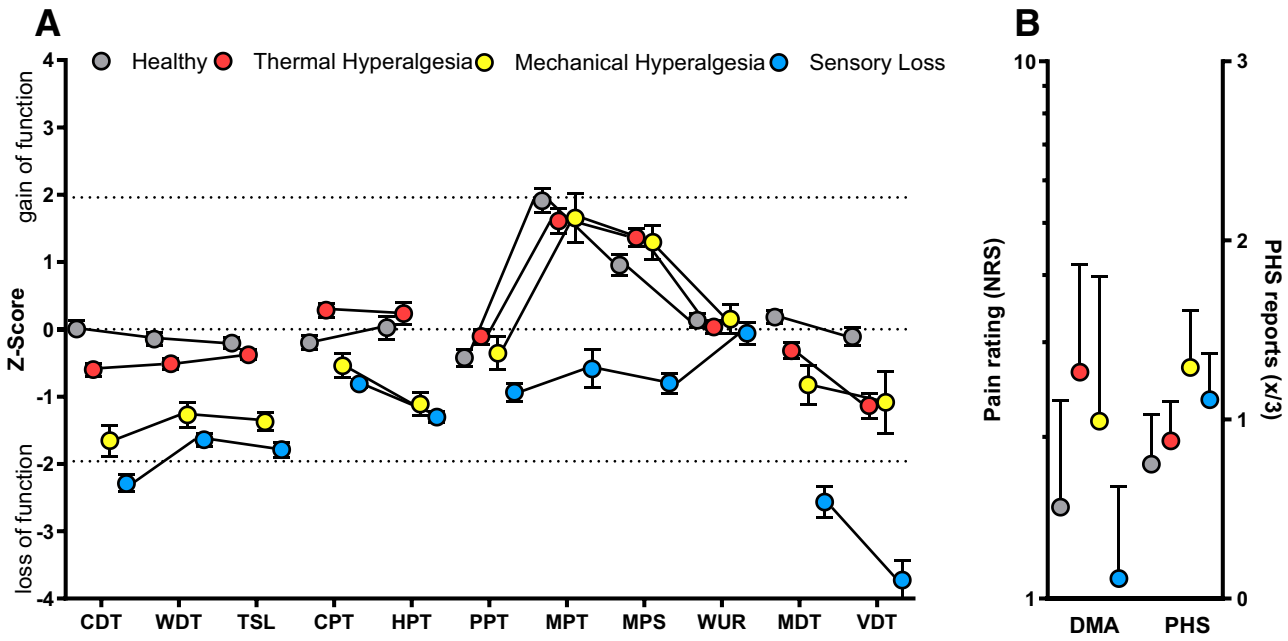


Figure 1—QST profile of the right foot of study participants, presented according to sensory phenotype (green = healthy, red = TH, yellow = MH, blue = SL). Values are means ± SEs. *A*: QST domains are grouped (from left to right) into thermal detection, thermal pain, mechanical pain, and mechanical detection. *B*: DMA and paradoxical heat sensation (PHS) are presented in the smaller right graph. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, numerical rating scale; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

peroneal and tibial motor nerves were impaired only among those with SL compared with all other groups. Sensitivity analyses yielded identical results (Supplementary Table 1).

Accordingly, the prevalence of DSPN based on both clinical criteria and the Toronto consensus definition showed a similar pattern of gradual increase across the groups; ∼61.8% and ∼79.8% of the SL group fulfilled the Toronto consensus and clinical criteria for DSPN, respectively, whereas the corresponding frequencies in the healthy group were 6.3% and 8.8%, respectively. Both TH and MH groups showed higher DSPN prevalence compared with healthy participants, whereas clinically defined DSPN was more prevalent in the MH group than in TH group (Table 1 and Fig. 3).

Among those with a DSPN diagnosis at baseline based on clinical (n = 111) or Toronto consensus criteria (confirmed DSPN; n = 81), the SL phenotype was most frequent (48.6% and 51.9%, respectively), followed by MH (21% and 27%, respectively) and TH (18% and 21%, respectively). As expected, the prevalence of the healthy phenotype was markedly low among those with DSPN according to either definition (6.3% and 6.2%, respectively) (Fig. 3).

Longitudinal Sensory Phenotypic Dynamics

Participants (n = 250 [79.1%]) underwent follow-up for 1, 2, and/or 4 years, for a mean duration of 2.88 ± 1.27 years. The rates as well as the durations of follow-up were similar across the four sensory phenotypes (85.0% vs. 74.7% vs. 81.8% vs. 75.0%; P = 0.287 and 3.11 vs. 2.83 vs. 2.72 vs. 2.81 years; P = 0.338, respectively). The main characteristics of those undergoing follow-up were similar to the sum of the initial cohort (Supplementary Table 2).

The phenotypic redistribution pattern is presented in Fig. 4. At the end of follow-up, compared with baseline, the percentage of those in the healthy cluster decreased (−41.2%), that of those in the SL group increased (+29.4%), and those of participants in the TH and MH groups increased slightly (+8.8% and +10.0%, respectively).

At the end of follow-up, 135 participants (54.0%) had shown a change of sensory phenotype (Fig. 5). The likelihood of a change of phenotype positively correlated with follow-up duration (OR 1.22; 95% CI 1.01–1.48; P = 0.044). The rate of change was lowest among those with SL at baseline (29.4% for SL vs. 58.8%, 60.3%, and 61.3% for healthy, TH, and MH, respectively; P = 0.001; corresponding ORs 3.43, 3.65, and 3.90; all $P < 0.002$).

There was a distinct pattern of change according to baseline phenotype (one-sample χ^2 $P < 0.05$) (Fig. 5). Those with an initial healthy phenotype changed more frequently to TH (62.5%; $P < 0.05$ vs. MH and SL), those starting as TH moved toward MH (58.5%; $P < 0.05$ vs. healthy and SL), and those starting as MH moved similarly toward TH and SL (46.2% and 43.6%, respectively; $P < 0.05$ vs. healthy). Those in the most stable cluster of SL at baseline changed most frequently toward MH (66.7%; $P < 0.01$ vs. healthy) (Fig. 5).

Table 1—Comparative presentation of demographic, clinical, laboratory, and neurological characteristics of four sensory phenotypes among individuals examined at baseline

	Healthy	TH	MH	SL	*P*
n (%)	80 (25.3)	91 (28.9)	77 (24.4)	68 (21.2)	
Age, years	53.7 ± 14.1	58.7 ± 15.1	61.6 ± 13.0**	64.6 ± 10.2***$	**<0.001**
Female sex	31 (38.8)	42 (46.2)	30 (39.0)	21 (30.9)	0.281
T2D	59 (73.8)	69 (75.8)	63 (81.8)	58 (85.3)	0.279
Diabetes duration, years	8.0 (1.0, 17.3)	10.0 (4.0, 7.8)	10.5 (5.0, 17.0)	10.0 (6.0, 20.0)	0.315
BMI, kg/m^2	30.5 ± 6.7	29.8 ± 5.4	28.8 ± 5.7	31.1 ± 5.9	0.113
WHR	0.96 ± 0.09	0.96 ± 0.09	0.97 ± 0.09	0.99 ± 0.10	0.080
HbA_{1c}					0.416
%	7.33 ± 1.42	7.40 ± 1.40	7.10 ± 1.23	7.44 ± 1.22	
mmol/mol	56.7 ± 15.6	57.3 ± 15.3	54.4 ± 13.5	57.8 ± 13.4	
eGFR CKD-EPI, mL/min	98.0 ± 17.2	88.9 ± 21.7*	90.2 ± 17.4	84.3 ± 20.7***	**<0.001**
Total cholesterol, mg/dL	206.2 ± 46.9	184.7 ± 44.3*	194.7 ± 47.0	179.9 ± 50.7**	**0.003**
LDL cholesterol, mg/dL	119.9 ± 41.5	100.0 ± 33.0**	111.3 ± 44.2	93.1 ± 33.8***#	**<0.001**
Cholesterol-lowering therapy	23 (28.8)	34 (37.4)	38 (49.4)**	39 (57.4)***$	**0.002**
Statin	23 (28.8)	34 (37.4)	38 (49.4)	38 (55.9)	
Ezetimibe	3 (3.8)	1 (1.1)	6 (7.8)	2 (2.9)	
Known CVD	15 (18.8)	27 (29.7)	21 (27.3)	26 (38.2)	0.070
Analgesic use	3 (3.8)	12 (13.2)*	6 (7.8)	15 (22.1)**#	**0.004**
Anticonvulsants	2 (2.5)	6 (6.6)	3 (3.9)	11 (16.2)	
TCA/SNRI	0 (0.0)	5 (5.5)	2 (2.6)	4 (5.9)	
Opioids	1 (1.3)	3 (3.3)	1 (1.3)	2 (2.9)	
NSS	0.0 (0.0, 5.0)	3.0 (0.0, 6.0)	5.0 (0.0, 7.0)**	5.0 (0.0, 7.0)***$	**<0.001**
NDS	0.0 (0.0, 2.0)	2.0 (0.0, 4.0)*	2.0 (2.0, 5.0)***	6.0 (4.8, 8.0)***$$$###	**<0.001**
Confirmed DSPN[a]	5 (6.3)	17 (18.7)*	17 (22.1)**	42 (61.8)***$$$###	**<0.001**
Clinical neuropathy[b]	7 (8.8)	21 (23.1)*	30 (39.0)***$	54 (79.8)***$$$##	**<0.001**
NCV suralis, m/s	45.1 ± 7.5	43.2 ± 8.4	41.1 ± 8.6*	36.6 ± 9.2***$$$#	**<0.001**
SNAP suralis, μV	6.3 ± 4.5	6.0 ± 6.1	3.9 ± 3.4**$	2.3 ± 2.6***$$$	**<0.001**
NCV common peroneal, m/s	42.1 ± 5.1	41.0 ± 6.4	40.6 ± 5.9	36.0 ± 7.3***$$$###	**<0.001**
CMAP peroneal, μV	7.0 ± 3.4	6.0 ± 3.5	5.7 ± 3.5	3.4 ± 2.8***$$$###	**<0.001**
NCV tibial, m/s	42.3 ± 5.1	41.3 ± 5.4	40.9 ± 5.0	37.3 ± 6.7***$$$##	**<0.001**
CMAP tibial, μV	15.0 ± 6.6	13.4 ± 7.4	12.4 ± 6.9	7.1 ± 6.3***$$$###	**<0.001**

Data are given as *n* (%), mean ± SD, or median (25th, 75th interquartile range). Bold font indicates statistical significance. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; SNRI, serotonin/norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; WHR, waist-to-hip ratio. [a]Confirmed DSPN according to Toronto consensus criteria (see *Research Design and Methods*). [b]Clinical DSPN defined based on NSS and NDS (see *Research Design and Methods*). *$#*P* < 0.05, **$$##*P* < 0.01, ***$$$###*P* < 0.001 for post hoc comparisons vs. healthy, TH, and MH after Bonferroni correction.

New Occurrence of Healthy and SL Phenotypes

On the basis of the findings of the cross-sectional analysis, we considered the healthy and SL phenotypes to be the extremes of the DSPN spectrum. Cox proportional hazards regression analysis was conducted for the first occurrence of SL among those without SL at baseline (*n* = 199), as well as for the first manifestation of a healthy phenotype among those with one of the three neuropathic phenotypes at baseline (*n* = 182).

There were 37 first occurrences of the SL phenotype, corresponding to an incidence of 6.35 cases per 100 patient-years. In unadjusted analysis, those with MH at baseline showed a risk ∼5.5-fold (HR 5.46; 95% CI 2.04–14.56; *P* = 0.001) that of healthy participants, and those with TH showed a risk ∼3.0-fold (HR 2.95; 95% CI 1.04–8.39; *P* = 0.042) (Table 2 and Supplementary Fig. 1). In the adjusted model, the baseline MH phenotype was consistently associated with an increased risk of SL occurrence (5.19; 95% CI 1.80–14.99; *P* = 0.002), whereas the magnitude of association with TH remained unchanged, although slightly statistically attenuated (2.87; 95% CI 0.97–8.53; *P* = 0.058) (Table 2). In the adjusted model, higher HbA_{1c} levels were also independently associated with a greater likelihood of SL occurrence (aHR 1.37; 95% CI 1.06–1.79; *P* = 0.018).

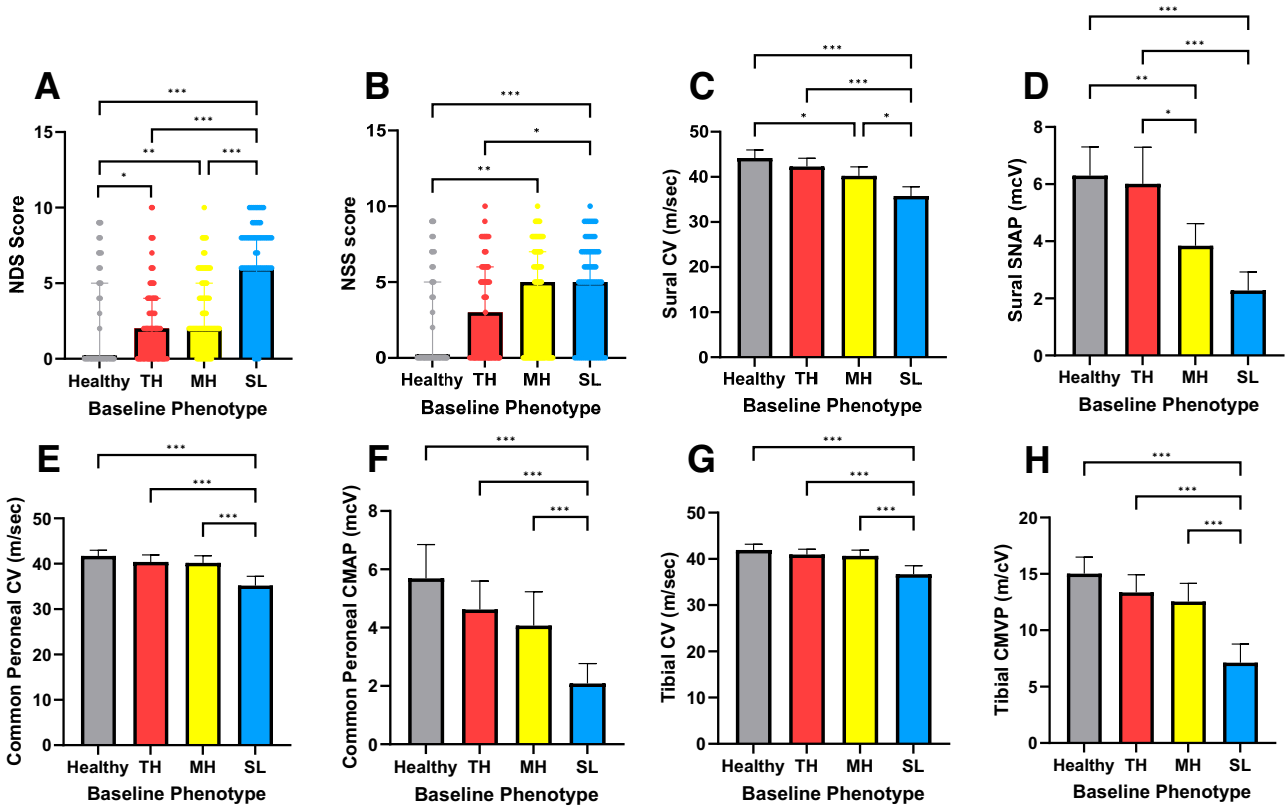


Figure 2—Comparison of clinical (*A* and *B*) and electrophysiological neurological (*C–H*) features among the four sensory phenotypes. CV, conduction velocity. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

There were 24 new occurrences of the healthy phenotype, corresponding to an incidence of 4.68 cases per 100 patient-years). The highest rates of reversion to healthy were noted among those with TH at baseline (HR 6.14 vs. SL; 95% CI 1.40–26.86; $P = 0.016$), whereas in individuals with MH, reversion rates were comparable to those of individuals with SL (HR 2.82; 95% CI 0.58–13.58; $P = 0.197$) (Table 2 and Supplementary Fig. 1). These findings were not substantially affected in the adjusted model (aHR 4.73 for TH vs. SL; 95% CI 1.01–22.03; $P = 0.048$) (Table 2).

High HbA_{1c} May Predict Longitudinal Progression or Reversion of Intermediate Phenotypes

We further analyzed those with TH or MH at baseline who showed either progression (toward MH/SL and SL, respectively; $n = 51$) or reversion (toward healthy and healthy/TH, respectively; $n = 29$) at the end of follow-up, as a measure of overall improvement or worsening of peripheral neurological status. In multivariable binary logistic regression including all previously mentioned factors, only higher HbA_{1c} showed a trend toward prediction of progression versus reversion (aOR 1.45; 95% CI 0.95–2.30; $P = 0.082$). When ascending HbA_{1c} quartiles were entered into the model instead, those in the highest quartile (median HbA_{1c} 8.4%; range 7.8–12.7%) showed a significantly higher risk of progression compared with those in the lowest quartile (median HbA_{1c} 5.9%; range 5.8–6.1%), although with a wide CI (aOR 24.78; 95% CI 2.30–266.76; $P = 0.008$).

Analysis including those who showed a stable phenotype at the end of follow-up yielded identical results (highest vs. lowest HbA_{1c} quartile: aOR 30.40; 95% CI 2.87–322.31; $P = 0.005$ for progression vs. no progression and aOR 0.040; 95% CI 0.01–0.43; $P = 0.008$ for reversion vs. no reversion).

Prospective Impact of Baseline Sensory Phenotype on DSPN Development

We further analyzed the occurrence of DSPN per baseline sensory phenotype among those without DSPN at baseline, according to both definitions described above ($n = 160$ and 184 for clinical and confirmed DSPN, respectively).

Occurrence of Clinically Defined DSPN

SL phenotype at baseline was associated with higher odds of clinical DSPN (HR 3.35 vs. healthy; 95% CI 1.09–10.26; $P = 0.034$), whereas TH and MH were not (HR 1.59; 95% CI 0.76–3.30; $P = 0.218$ and HR 1.62; 95% CI 0.73–3.63; $P = 0.239$, respectively) (Table 3 and Supplementary Fig. 2). These findings were replicated in the adjusted model (aHR 3.62; 95% CI 1.07–12.30; $P = 0.034$).

Analysis among those without the SL sensory phenotype at baseline ($n = 149$ [healthy $n = 62$, TH $n = 50$, and MH $n = 37$]) revealed that those who developed SL in the

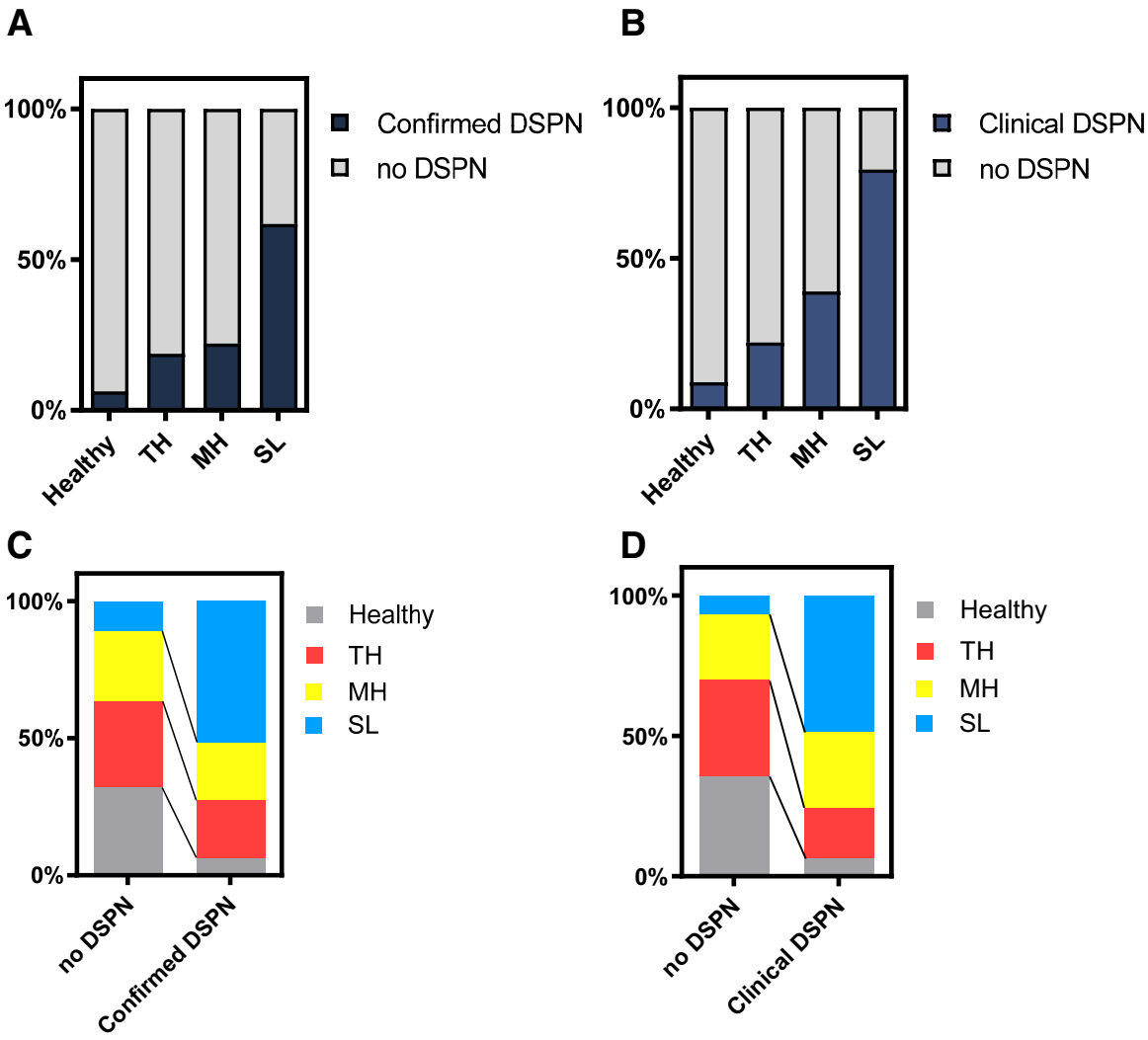


Figure 3—*A* and *B*: Prevalence of DSPN among the four sensory phenotypes, according to the Toronto consensus definition for confirmed DSPN (*A*) and clinical criteria (*B*). *C* and *D*: Sensory phenotypic frequencies among those with and without DSPN, according to the definitions for confirmed (*C*) and clinical DSPN (*D*).

course of follow-up showed a threefold higher risk of clinical DSPN development than those who did not (HR 3.15; 95% CI 1.53–6.48; P = 0.002) (Supplementary Fig. 2), an effect that was independent of baseline sensory phenotype (aHR 3.13; 95% CI 1.52–6.43; P = 0.002) and remained unaffected in the fully adjusted model (aHR 3.48; 95% CI 1.43–8.54; P = 0.006).

Occurrence of Confirmed DSPN According to Toronto Criteria

SL phenotype at baseline was associated with higher odds of confirmed DSPN development (HR 5.15 vs. healthy; 95% CI 1.63–16.31; P = 0.005), whereas TH and MH were not (HR 0.57; 95% CI 0.14–2.29; P = 0.429 and HR 1.57; 95% CI 0.50–4.90; P = 0.436, respectively) (Table 3). This association remained significant in the adjusted model (aHR 3.90; 95% CI 1.21–15.12; P = 0.022 and aHR 4.66; 95% CI 1.16–18.68; P = 0.030, respectively). Higher baseline HbA_{1c} values were again associated with higher risk of DSPN development (HR 1.45; 95% CI 1.01–2.10; P = 0.046).

Analysis among those without the SL sensory phenotype at baseline (n = 167 [healthy n = 65, TH n = 56, and MH n = 46]) revealed that those who developed SL in the course of follow-up showed a roughly threefold higher risk of confirmed DSPN development than those who did not (HR 3.18; 95% CI 1.06–9.55; P = 0.039) (Table 3 and Supplementary Fig. 2), an effect that was also independent of baseline sensory phenotype (aHR 3.15; 95% CI 1.00–9.93; P = 0.050) but was attenuated in the fully-adjusted model (aHR 2.59; 95% CI 0.70–9.60; P = 0.154).

DISCUSSION

The current study provides new insight into the natural course of sensory changes that culminate in the full-blown

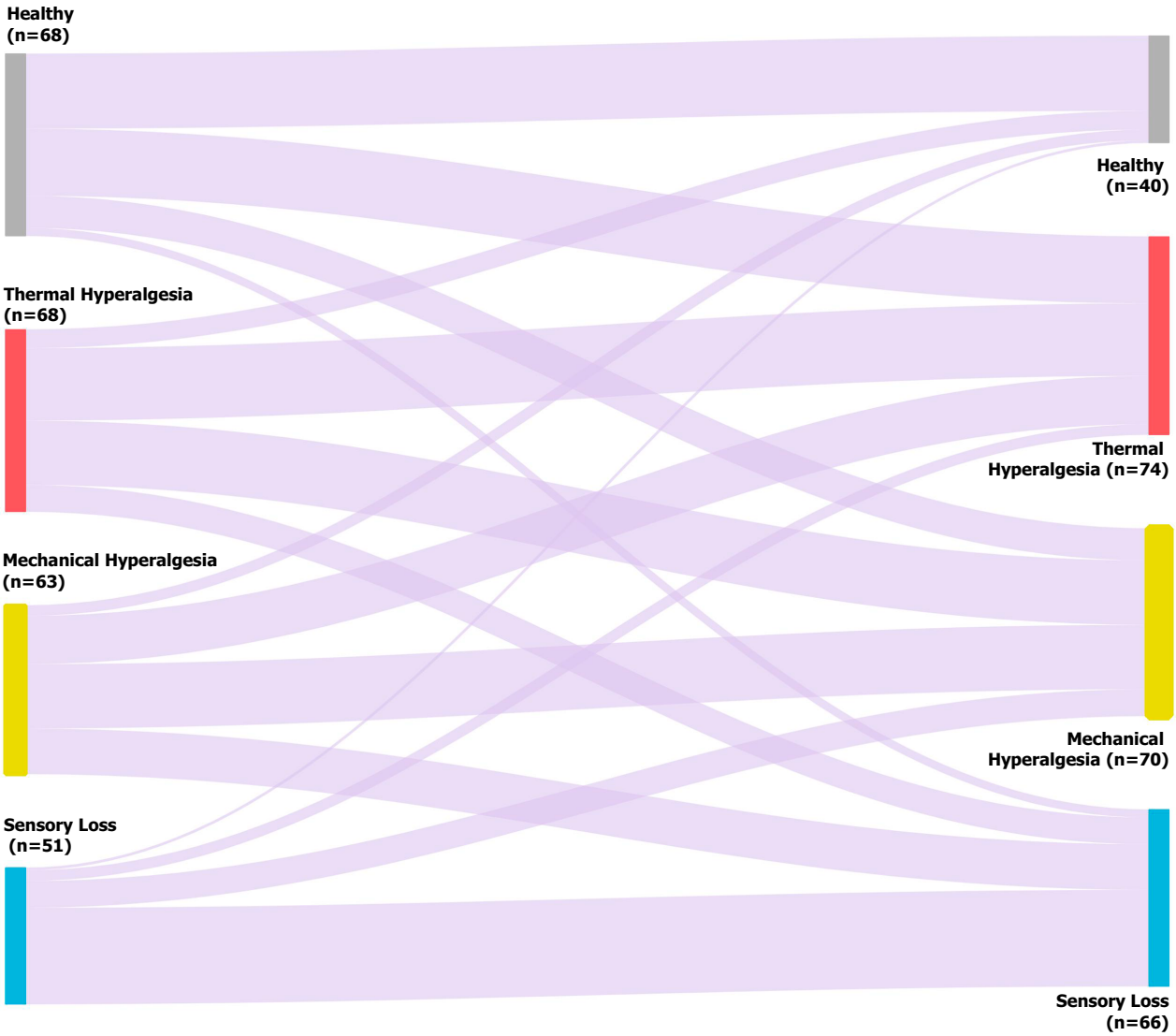


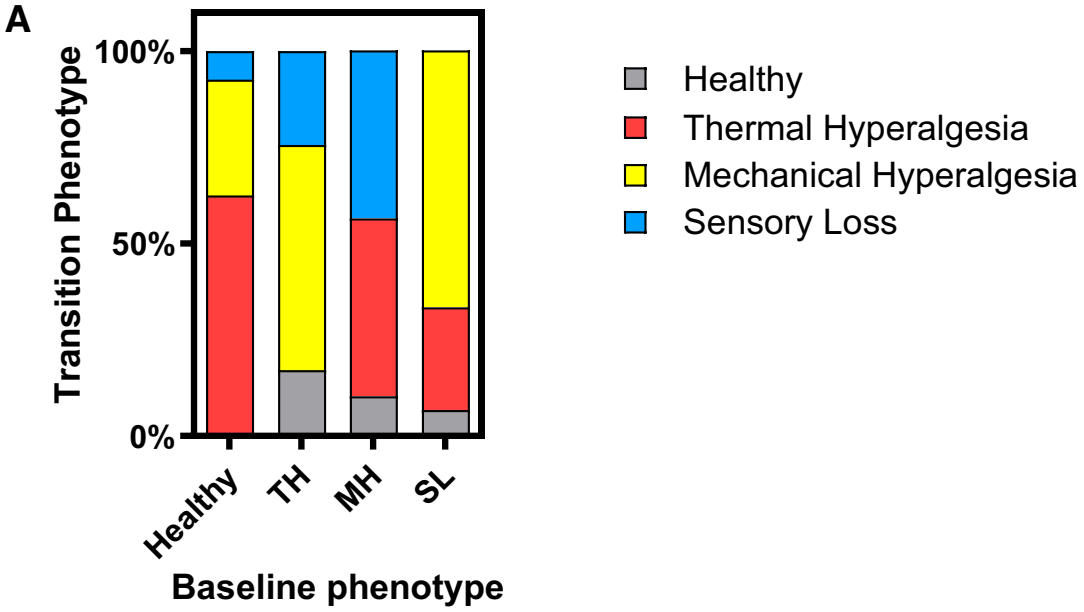
Figure 4—Sankey diagram of redistribution of foot sensory phenotypes among participants undergoing follow-up (n = 250), revealing an overall decrease in healthy and increase in SL prevalence during the course of follow-up, with relatively stable frequencies of TH and MH.

state of DSPN. Our findings are consistent with a continuously increasing severity of neuropathic findings across healthy, TH, MH, and SL groups, likely reflecting progressive loss of fiber density. We suggest that SL showing the lowest rate of transition to other phenotypes represents an end stage of DSPN, which is also reflected by the fact that SL is the most frequent sensory phenotype in DSPN, followed by MH and TH (8,9). Furthermore, sensory phenotypes exhibit a patterned order of longitudinal appearance in diabetes, beginning with healthy status and culminating in SL. TH and MH may represent intermediate states preceding SL, whereas TH additionally shows a greater probability of reversion to the healthy status. At this transitional stage, higher HbA_{1c} values may predispose to progression and/or hinder regression of sensory impairment. Finally, among those not fulfilling criteria for DSPN, presence of the SL phenotype at baseline or development of new SL is independently associated with future DSPN occurrence.

DSPN constitutes a predominantly axonal peripheral nerve disorder. The progressive loss of small and large fibers in DSPN results from fiber degeneration and/or impaired regeneration (18,19) and correlates with gradually diminishing action potential of affected nerves (20). A number of previous studies have longitudinally examined the development of DSPN in patient cohorts (21–29) using a variety of small and/or large fiber assessments. Nevertheless, there is a profound lack of evidence to establish a model of the natural history of DSPN development from early stages, in order to improve the understanding of the time course of DSPN-related changes, with the ultimate goal of the early identification of patients at risk and those most likely to benefit from therapeutic interventions.

In contrast to previous QST-based approaches in patients with diabetes, which have used an approach based on absolute abnormalities of isolated QST parameters (z scores ≥ 2 or ≤ 2) in patients with painful or nonpainful

A



B

Baseline Phenotype \ Transition Phenotype	Healthy	TH	MH	SL	
Healthy		**25 (62.5) 8.3-fold vs. SL 2.1-fold vs. MH**	12 (30.0)$	3 (7.5)$$$#	**<0.001**
TH	7 (17.1)		**24 (58.5)**** **3.4-fold vs. Healthy 2.4-fold vs. SL**	10 (24.4)#	**0.002**
MH	4 (10.3)	**18 (46.2)**** **4.5-fold vs. Healthy**		**17 (43.6)**** **4.3-fold vs. Healthy**	**0.009**
SL	1 (6.7)	4 (26.7)	**10 (66.7)**** **10-fold vs. Healthy 2.5-fold vs. TH**		**0.015**

Figure 5—*A*: Frequencies of phenotypic transition among participants showing a phenotypic change at the end of follow-up. *B*: Changes occurred predominantly from healthy to TH, from TH to MH, from MH to either TH or SL, and from SL to MH. Values are *n* (%). *P* values and post hoc tests are derived from a one-sample χ^2 test. $\#P < 0.05$, $**P < 0.01$, $\$\$\$P < 0.001$ for post hoc comparisons vs. healthy, TH, and MH after Bonferroni correction.

DSPN (30–32) or have primarily focused on sensory phenotyping in already established DSPN (8,9,11), we followed the reverse process of phenotyping a well-characterized cohort of individuals with diabetes via clinical and electrophysiological tools, without a priori assumptions regarding their DSPN status. We attempted to characterize DSPN

Table 2—Crude and aHRs for new occurrence of SL and healthy phenotypes according to baseline sensory phenotype

Baseline senory phenotype	SL phenotype occurrence				Healthy phenotype occurrence			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI) vs. healthy	*P*	HR (95% CI) vs. healthy	*P*	HR (95% CI) vs. SL	*P*	HR (95% CI) vs. SL	*P*
TH	2.95 (1.04–8.39)	**0.042**	2.87 (0.97–8.53)	**0.058**	5.88 (1.35–25.74)	**0.019**	4.73 (1.01–22.03)	**0.048**
MH	5.46 (2.04–14.56)	**0.001**	5.19 (1.80–14.99)	**0.002**	2.72 (0.57–13.11)	0.212	2.03 (0.40–10.30)	0.395

Data were adjusted for age, sex, diabetes type, diabetes duration, BMI, waist-to-hip ratio, eGFR, HbA_{1c}, cholesterol, known cardiovascular disease, use of cholesterol-lowering medication, and use of analgesics. Bold font indicates statistical significance.

Table 3—Crude and aHRs for new occurrence of DSPN per baseline sensory phenotype

Baseline sensory phenotype	Clinical DSPN occurrence				Confirmed DSPN occurrence			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI) vs. healthy	*P*	HR (95% CI) vs. healthy	*P*	HR (95% CI) vs. healthy	*P*	HR (95% CI) vs. healthy	*P*
TH	1.59 (0.76–3.30)	0.218	1.10 (0.49–2.51)	0.815	0.57 (0.14–2.29)	0.429	0.42 (0.09–1.94)	0.268
MH	1.62 (1.73–3.63)	0.239	1.02 (0.39–2.68)	0.966	1.57 (0.50–4.90)	0.436	1.22 (0.34–4.32)	0.760
SL	3.35 (1.09–10.26)	**0.034**	3.62 (1.07–12.30)	**0.039**	5.15 (1.63–16.31)	**0.005**	4.66 (1.16–18.68)	**0.030**

DSPN defined by clinical criteria or Toronto consensus definition for confirmed DSPN. Data were adjusted for age, sex, diabetes type, diabetes duration, BMI, waist-to-hip ratio, eGFR, HbA_{1c}, cholesterol, known cardiovascular disease, use of cholesterol-lowering medication, and use of analgesics. Bold font indicates statistical significance.

simultaneously with sensory phenotyping in each examination. This not only served the objective assessment of neuropathic findings within patient groups with distinct sensory features, but also allowed for the investigation of the relationship between sensory phenotypic evolution and new DSPN development in the course of time.

The SL phenotype showed the highest longitudinal stability, exhibiting a 3.5- to 4-fold lower probability of change during the course of follow-up compared with the other subgroups. Furthermore, motor impairment was observed exclusively in SL (Table 1 and Fig. 1). This evidence further supports that QST-defined SL is not merely a clinical subtype of DSPN, as may have previously been suggested (8,9), but rather represents the terminal conclusion of the dynamic changes of neural function and/or structure in DSPN.

Furthermore, it has been previously demonstrated that a considerable fraction of findings consistent with DSPN may be reversible in the long term. Results from the ADDITION-Denmark study reported similar rates of progression and regression of symptoms (23% and 26%, respectively) assessed through the Michigan Neuropathy Screening Instrument questionnaire when patients initially newly diagnosed with T2D were examined 13 years after diagnosis (27). It should be noted that the initial hypothesis of this study included a sequential small, mixed, and finally large fiber–related symptom appearance, culminating in sensory loss; however, this was not confirmed by the findings, possibly because of the limitations related to the use of the Michigan Neuropathy Screening Instrument questionnaire (27). Recently published results of the German Diabetes Study, implementing multiple small and large fiber measures, including IENFD, also indicated considerable rates of progression as well as regression of various peripheral neural measures among patients 5 years after the first diagnosis of diabetes (26). Another longitudinal study by Løseth et al. (33) reported higher rates of small fiber damage progression (assessed by IENFD and thermal detection thresholds) for T2D compared with T1D within 5 years of follow-up, whereas progression of large fiber damage was overall small. Notably, none of these studies were able to identify factors associated with progression or regression of peripheral neurological impairment (26,33).

The pattern of longitudinal phenotypic switch that emerged in our study provides the first clinical evidence of a concept of the DSPN natural course based on clinical sensory phenotypes. From a pathophysiological standpoint, TH corresponds to a state of primary hyperalgesia (peripheral sensitization), characterized by retained sensory function with heat pain hypersensitivity and/or allodynia. MH shows attributes of secondary hyperalgesia (central sensitization through various putative mechanisms, including partial denervation), with reduced thermal sensation, hypersensitivity to mechanical painful stimuli, and allodynia. SL is characterized by loss of thermal and mechanical sensations, similar to that observed in nerve block or denervation (10). The observed initial change from healthy status toward TH (primary hyperalgesia) likely represents a functional and potentially reversible phenomenon. This can be attributed to nociceptor sensitization (34,35) through various mechanisms pertinent to the dysmetabolic environment in diabetes, including but not limited to hyperglycemia (36,37). A progressive loss of fiber density, reflected by the steep decrease of SNAP compared with TH, marks the transition toward the MH phenotype, which is consistent with a pattern of secondary hyperalgesia. This phenomenon may be primarily related to a loss of predominantly small fibers that mediate thermal sensation and pain, leaving features of MH in the foreground or secondary to the partial peripheral denervation and adjacent surviving nociceptor sensitization (38). Lastly, the loss of critical axonal mass marks the transition to the SL phenotype. Expectedly, it is also at this stage that peripheral neural damage is most likely to reach the threshold for a DSPN diagnosis to be established, while concomitantly, motor neural impairment starts to become apparent.

In the current study, higher baseline HbA_{1c} values were found to be independently associated with a greater likelihood of the occurrence of new DSPN and SL phenotype, as well as with higher rates of progression and lower rates of regression of TH/MH. Although it could be argued that this finding advocates for tighter glycemic control to prevent DSPN progression, which is of proven value among patients with T1D, the evidence for T2D is less convincing (39). Additionally, it is unclear if this observation

corresponds to a direct effect of poor glycemic control or is confounded by other underlying metabolic factors contributing to higher HbA_{1c} or even by the greater odds that these patients have a rapid HbA_{1c} decrease in the course of their treatment, which is itself a known risk factor for DSPN (40).

The current study has certain limitations. The follow-up duration of roughly 3 years is rather short, although at the same time, it allowed for close observation of phenotypic change dynamics. Apart from QST, we lacked other measures of small fiber assessment, such as IENFD, corneal confocal microscopy, or c-fiber stimulation, to further validate our results. Another limitation concerns the lack of assessment of neuropathic pain through pain scales or questionnaires. A minority of our patients (11.4%) received medication against neuropathic pain, and the degree to which this could have influenced our results cannot be estimated; however, we conducted statistical adjustments for analgesic therapy in multivariable analyses, and this fact renders our results more directly translatable into real-world clinical practice.

In summary, we provide new evidence on the features and time evolution of lower-extremity sensory phenotypes in diabetes, which additionally supports the previously hypothetical views on the natural history of DSPN. Sensory phenotypes exhibit an increasing severity and patterned order of longitudinal appearance in diabetes reflecting progressive nerve fiber loss, beginning with healthy status and culminating in SL. TH and MH may represent intermediate states in DSPN development, although TH may revert to healthy status. An important implication of the presented findings is that QST-based sensory clustering may be useful in identifying patients in a prediagnostic stage of neural impairment, characterized by at least partial reversibility, using standardized algorithms. This could help guide preventive strategies (e.g., optimization of glycemic control) or candidate causative therapies in patients in those dynamic stages. Furthermore, serial phenotyping could potentially be useful in assessing the effectiveness of specific therapies by determining reversion to healthy status or an earlier sensory phenotype. Further corroboration of our findings in independent cohorts will be required to allow for the integration of approaches using QST-based sensory phenotyping into clinical practice. Future prospective observational studies focusing on hard DSPN-related end points (e.g., foot ulcerations/amputations) and approaches investigating the efficacy of preventive or therapeutic interventions in patients exhibiting different sensory phenotypes are necessary to further support our results.

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Author Contributions. D.T., S.K., and Z.K. conceived the idea for this manuscript. D.T. and Z.K. were involved in data collection and curation, conducted the statistical analysis, and wrote the manuscript. L.Sc., E.v.R., A.S., and L.Se. recruited patients, performed the examinations, and collected the data. S.H., J.S., and S.K. supervised the project and edited the manuscript. All authors reviewed and approved the final version of the manuscript. D.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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