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Changes Over 10 Years in Peripheral Nerve Function in People With Well-Controlled Type 2 Diabetes and Those With Normal Glucose Tolerance

Alexander Strom,[1,2] Klaus Strassburger,[3] Dan Ziegler,[1] Gundega Sipola,[1] Katsiaryna Prystupa,[1,2] Robert Wagner,[1,2,4] Michael Roden,[1,2,4] and Gidon J. Bönhof,[1,2,4] for the GDS Group

Correspondence
Dr. Strom
alexander.strom@ddz.de

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Abstract

Background and Objectives

There is a lack of knowledge on the changes in peripheral nerve function in people with well-controlled, recently diagnosed type 2 diabetes compared with those with normal glucose tolerance (NGT). In this study, we aimed to investigate the natural course of the function of lower extremity small and large nerve fibers in people with NGT and its decline in those with well-controlled type 2 diabetes.

Methods

This prospective observational study assessed changes in nerve function in participants of the German Diabetes Study with recently diagnosed (≤1 year) type 2 diabetes and age-matched and sex-matched individuals with NGT after 5 years and in a larger group of participants with type 2 diabetes after 5 and 10 years. Reference tests of lower extremity peripheral nerve function included peroneal motor nerve conduction velocity (MNCV) and sural sensory nerve conduction velocity (SNCV), sural sensory nerve action potential (SNAP), malleolar vibration perception threshold (VPT), and thermal detection thresholds (TDTs). Data were analyzed using multiple linear or logistic regression analyses.

Results

At baseline, all 5 nerve function measures showed impairment in the 52 individuals in the diabetes group (33% female, median age 51.7 years) compared with the 52 individuals in the matched NGT group (33% female, median age 51.4 years). After 5 years, 2 nerve indices declined in the diabetes group (peroneal MNCV and VPT) and 3 in the NGT group (peroneal MNCV, VPT, and TDT for cold), with similar 5-year declines observed in both groups after adjustment for baseline values and pairwise matching. In addition, the Neuropathy Disability Score increased in the NGT group but not in the diabetes group. Comparable patterns of decline after 5 and 10 years were found in the larger diabetes cohort of 141 individuals (39% female, median baseline age 53.6 years). The observed 10-year prevalence of abnormal NCVs closely matched estimates based on natural aging-related decline (14.2% vs 12.8% for peroneal MNCV and 30.2% vs 31.0% for sural SNCV).

Discussion

These findings suggest that nerve function deterioration in well-controlled type 2 diabetes is primarily influenced by nerve function status at diagnosis and physiologic aging, rather than diabetes-related progression.

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Supplementary Material

[1]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich-Heine-University Düsseldorf, Germany; [2]German Center for Diabetes Research, Partner Düsseldorf, München-Neuherberg, Germany; [3]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany; and [4]Department of Endocrinology and Diabetology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany.

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Glossary

DSPN = diabetic sensorimotor polyneuropathy; **GDS** = German Diabetes Study; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **MNCV** = motor nerve conduction velocity; **NCS** = nerve conduction study; **NDS** = Neuropathy Disability Score; **NGT** = normal glucose tolerance; **NSS** = Neuropathy Symptom Score; **QST** = quantitative sensory testing; **SNAP** = sensory nerve action potential; **SNCV** = sensory nerve conduction velocity; **TDTs** = thermal detection thresholds; **VPT** = vibration perception threshold.

Introduction

As of today, more than 500 million people worldwide have diabetes mellitus, and that number is projected to exceed 1.3 billion by 2050.[1] Diabetic neuropathy is one of the most prevalent chronic complications of diabetes,[2,3] of which diabetic sensorimotor polyneuropathy (DSPN) represents the most relevant clinical manifestation. DSPN has been defined as a symmetrical, length-dependent impairment of sensorimotor nerve fibers attributable to metabolic and microvascular changes resulting from chronic exposure to hyperglycemia (diabetes) and cardiovascular risk covariates.[4] DSPN affects approximately 30% of people with diabetes (approximately 150 million people worldwide) and has an incidence of approximately 2% per year.[3,5] The prevalence of peripheral neuropathy in the older Western population with normal glucose tolerance (NGT) is less than 10%.[6] By contrast, more than 50% of people with diabetes will develop DSPN during their lifetime.[7] With its major clinical sequelae such as neuropathic pain, foot ulcers, and lower-limb amputations, DSPN is responsible for significant morbidity, increased risk of mortality, reduced quality of life, and increased health care costs.[3]

We have previously shown that peripheral nerve fiber impairment can be detected in approximately 20% of people as early as within the first year after diagnosis of type 2 diabetes, and that further peripheral nerve pathology and dysfunction develops over the following 5 years despite good glycemic control, with a significant degree of reversibility of the initial nerve changes.[8] Several other contemporary cohorts have also reported such remarkably high prevalence rates of DSPN in the early phase of type 2 diabetes.[9,10] However, it remains a conundrum why the prevalence of DSPN in type 2 diabetes remains high despite continuous improvements in diabetes care[9] and why, in contrast to type 1 diabetes, long-term intensive diabetes therapy and multifactorial risk intervention trials have failed to demonstrate a meaningful reduction in the incidence or progression rates of DSPN.[11]

DSPN is considered a heterogeneous disease with different clinical manifestations and different patterns of nerve fiber damage. According to current consensus criteria,[12] nerve conduction studies (NCSs), a well-established tool for detecting various peripheral nerve disorders, are the gold standard method for confirming the diagnosis of DSPN and assessing disease severity. Other nerve function tests include quantitative sensory testing (QST) to monitor sensory nerve function in response to controlled stimuli as well as clinical questionnaires to assess signs and symptoms of neuropathy.[11] Higher age is strongly associated with a deterioration of nerve function[13,14] and represents a risk factor for the development of DSPN.[15,16] However, there is currently a gap in knowledge about the extent and timing of long-term nerve function decline in people with recently diagnosed type 2 diabetes, particularly those with near-normoglycemic control, compared with those with NGT.

To pave the way for more accurate disease prediction and intervention strategies that take into account the influence of aging and modifiable cardiometabolic risk factors, we aimed to (1) determine the natural decline of peripheral nerve function using gold standard tests in people with NGT and in individuals with well-controlled, recently diagnosed type 2 diabetes after 5 years; (2) compare the time course of peripheral nerve function during the first 5 and 10 years of type 2 diabetes; and (3) evaluate the predictive value of physiologic aging-related nerve function decline for the changes in peripheral nerve function over the first 10 years of type 2 diabetes.

Methods

Study Participants

Individuals with recently diagnosed type 2 diabetes (known duration of diabetes ≤1 year) and NGT were recruited consecutively from the German Diabetes Study (GDS), an ongoing prospective observational study investigating the natural history of metabolic changes in diabetes and the development of chronic diabetic complications (ClinicalTrial.gov registration number: NCT01055093).[17] A detailed description of the study design and cohort profile of the GDS has been reported previously.[17] This prospective analysis included 52 individuals with type 2 diabetes and 52 individuals with NGT, matched 1:1 for sex and age, who had a 5-year follow-up (eFigure 1). Furthermore, changes in nerve function were assessed in 141 individuals with type 2 diabetes who underwent at the time point of this analysis both 5-year and 10-year follow-up examinations (eFigure 1).

Standard Protocols

The study was approved by the local ethics committee of Heinrich Heine University, Düsseldorf, Germany (No. 4508), and written informed consent was obtained from all participants before enrollment.

Peripheral Nerve Function

Electrophysiologic testing, QST, and clinical neuropathy assessment were performed as previously described.[18] In brief, motor nerve conduction velocity (MNCV) was measured in the peroneal nerve while sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) were measured in the sural nerve at a skin temperature of 33–34°C using surface electrodes. Vibration perception threshold (VPT) was determined at the right medial malleolus using the method of limits. Thermal detection thresholds (TDTs) to warm and cold stimuli were determined at the dorsum of the foot using the method of limits. Neurologic examination was performed using the Neuropathy Disability Score (NDS) while neuropathic symptoms were assessed using the Neuropathy Symptom Score (NSS).[19] DSPN was diagnosed using electrophysiologic (only lower extremities) and clinical criteria according to Toronto consensus criteria.[12] In brief, DSPN staging was defined as follows: subclinical DSPN (stage 1a): NDS ≤ 2 points, NSS ≤ 2 points, and NCS (peroneal MNCV, sural SNCV, and sural SNAP) < 2.5th percentile; confirmed asymptomatic DSPN (stage 1b): NDS ≥ 3 points, NSS ≤ 2 points, and NCS < 2.5th percentile; and confirmed symptomatic DSPN (stage 2): NSS ≥ 3 points and NCS < 2.5th percentile. Sex-specific normal ranges for NCV, SNAP, VPT, and TDT were used as previously reported.[8]

Laboratory Analyses

Plasma glucose, HbA1c, M-value, hsCRP, cholesterol (total, high-density lipoprotein [HDL], low-density lipoprotein [LDL]), serum triglycerides, and creatinine were measured as described before.[17]

Statistical Analysis

Data are presented as mean ± SD, median (first and third quartiles), or percentage. Within-participant changes were assessed using the Wilcoxon signed rank test (continuous data) or McNemar test (binary data). Correlations between 2 variables were determined using Spearman rank correlation analyses. Differences in slopes and intercepts between the NGT and type 2 diabetes groups were analyzed using multiple linear or logistic regression analyses with adjustment for potential confounders. For these analyses, skewed distributed variables were log-transformed. All statistical tests were two-sided, and the level of significance was set at $\alpha = 0.05$. Statistical analyses were performed with SPSS (version 22.0) and SAS (version 9.4) software.

Data Availability

The data sets generated during and/or analyzed during this study are not publicly available because of ethical constraints in consideration of participants' privacy and intellectual property protection but are available from the corresponding author on reasonable request.

Results

Baseline and 5-Year Follow-Up Demographic and Clinical Characteristics in Matched Participants With NGT and Type 2 Diabetes

Baseline and 5-year follow-up demographic and clinical characteristics of 52 pairwise sex-matched and age-matched participants with NGT and type 2 diabetes are provided in

Table 1 Neurophysiologic Parameters and Clinical Scores in the Prospective NGT and Type 2 Diabetes Groups

	NGT (n = 52)			Type 2 diabetes (n = 52)		
	N	Baseline	5 Y	N	Baseline	5 Y
Peroneal MNCV (m/s)	51	47.0 (44.0, 49.0)	45.0 (43.0, 48.3)[a]	52	45.0 (40.3, 48.1)	44.0 (40.3, 46.8)[a,b]
Sural SNCV (m/s)	46	46.5 (44.0, 50.3)	46.2 (42.0, 49.0)	51	46.0 (42.0, 50.0)	46.0 (40.0, 50.0)
Sural SNAP (μV)	46	10.2 (7.5, 12.4)	9.4 (4.6, 14.0)	51	6.9 (5.4, 9.8)	7.1 (4.8, 10.2)
VPT (μm)	49	0.82 (0.45, 1.61)	0.93 (0.61, 1.92)[a]	43	1.05 (0.56, 2.35)	1.63 (0.96, 4.48)[a,b]
TDT for cold (◦C)	46	29.4 (26.8, 30.3)	27.4 (26.2, 29.4)[a]	47	29.5 (27.3, 30.4)	28.6 (27.7, 29.5)
TDT for warm (◦C)	46	38.5 (36.3, 41.6)	39.3 (36.8, 41.9)	47	37.9 (36.4, 42.3)	39.8 (36.9, 42.4)
Neuropathy Symptom Score (NSS) (points)	47	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	49	0.00 (0.00, 0.00)	0.00 (0.00, 5.00)[b]
Neuropathy Disability Score (NDS) (points)	46	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)[a]	50	1.00 (0.00, 3.00)	2.00 (0.00, 4.00)[b]
Total DSPN (%)*	38	0.0	0.0	47	10.7	8.5
Subclinical DSPN (stage 1a)		0.0	0.0		4.3	2.1
Confirmed asymptomatic DSPN (stage 1b)		0.0	0.0		2.1	2.1
Confirmed DSPN (stage 2)		0.0	0.0		4.3	4.3

Abbreviations: MNCV = motor nerve conduction velocity; N = number of participants with prospective data for the corresponding variable; SNAP = sensory nerve action potential; SNCV = sensory nerve conduction velocity; TDT = thermal detection threshold; VPT = vibration perception threshold.
Data are % or median (first, third quartile).
[a] $p < 0.05$ vs baseline
[b] $p < 0.05$ vs NGT follow-up (Wilcoxon signed rank test and *McNemar test).

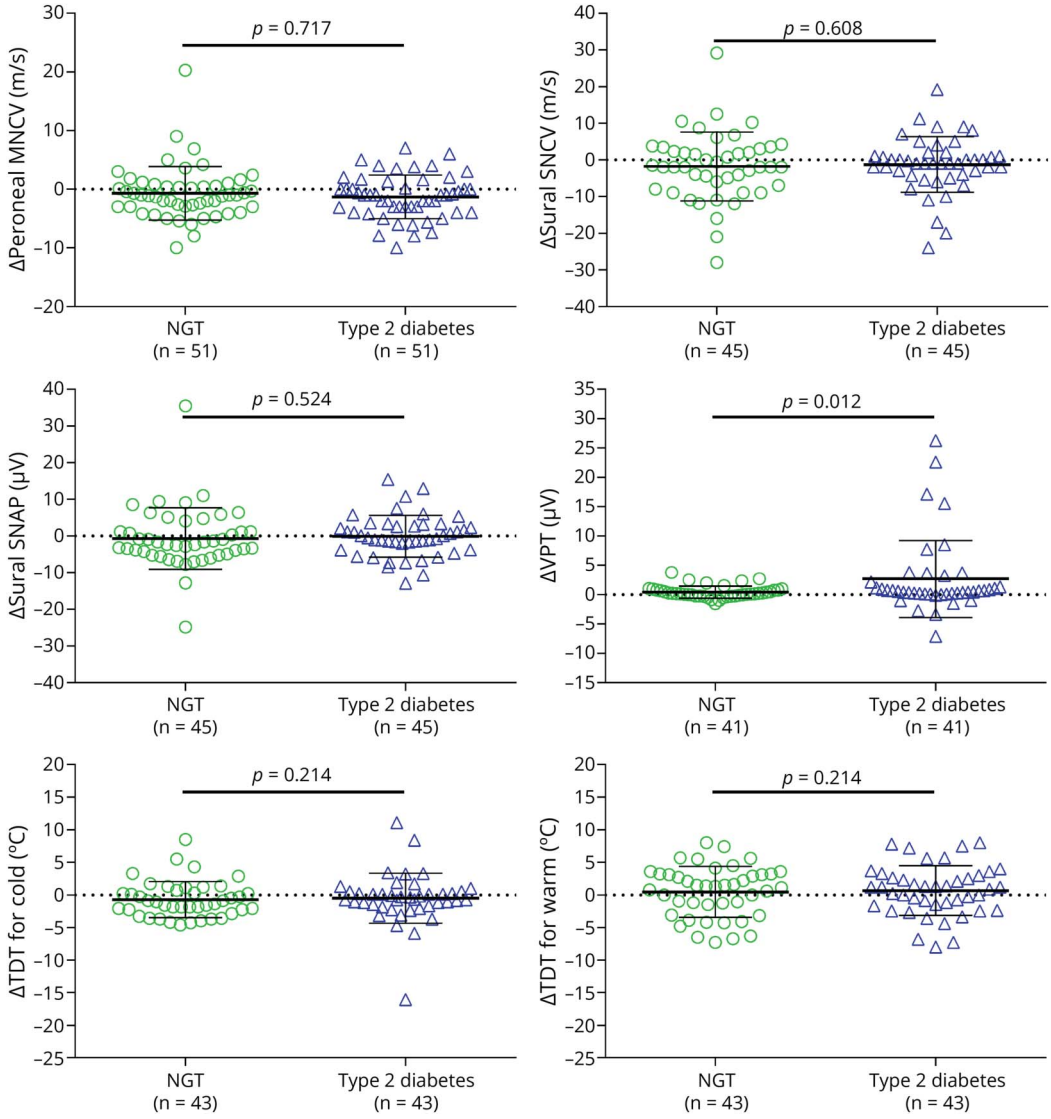
eTable 1. At 5 years, BMI was increased while total cholesterol and M-value were decreased in individuals with NGT (all $p < 0.05$). In the type 2 diabetes group, triglycerides, HbA1c, and fasting blood glucose were increased while height and hsCRP levels decreased after 5 years (all $p < 0.05$). No changes were observed in the remaining variables after 5 years. eFigure 2 shows the differences in age and BMI of the matched pairs.

Peripheral Nerve Function in NGT vs Type 2 Diabetes Groups at Baseline and After 5 Years

The median values of lower extremity peripheral nerve indices and clinical neuropathy scores and the prevalence of DSPN at baseline and after 5 years for participants with NGT and type 2 diabetes are presented in Table 1. In individuals with NGT, VPT and NDS increased while peroneal MNCV and cold TDT decreased after 5 years (all $p < 0.05$). In the type 2 diabetes group, VPT increased and peroneal MNCV decreased after 5 years (all $p < 0.05$). No changes were observed in the remaining variables after 5 years. Figure 1 illustrates the individual changes in peripheral nerve function indices after 5 years.

In the unadjusted model, the increase in VPT was higher in the type 2 diabetes group compared with the NGT group ($p = 0.012$) while changes in the other 5 peripheral nerve tests were similar between the 2 groups. Multivariate analyses of covariance (adjusted for corresponding baseline values, height, BMI, and matching) revealed no differences in the intercepts between the NGT and type 2 diabetes groups in any of the 6 nerve function indices (eTable 2). However, for sural SNCV and cold TDT, the test for equal slopes indicated differences regarding baseline values (eTable 2).

Figure 1 Individual Changes in Nerve Function Indices After 5 Years in People With Normal Glucose Tolerance and Type 2 Diabetes



Bars are mean ± SD. Differences between the groups were assessed using the Wilcoxon signed rank test.

To explore whether older age was associated with greater decline in nerve function, 5-year changes in nerve function were plotted against baseline age. Linear regression analyses showed that, except for VPT in the NGT group, no other parameters were associated with age in either group (Figure 2).

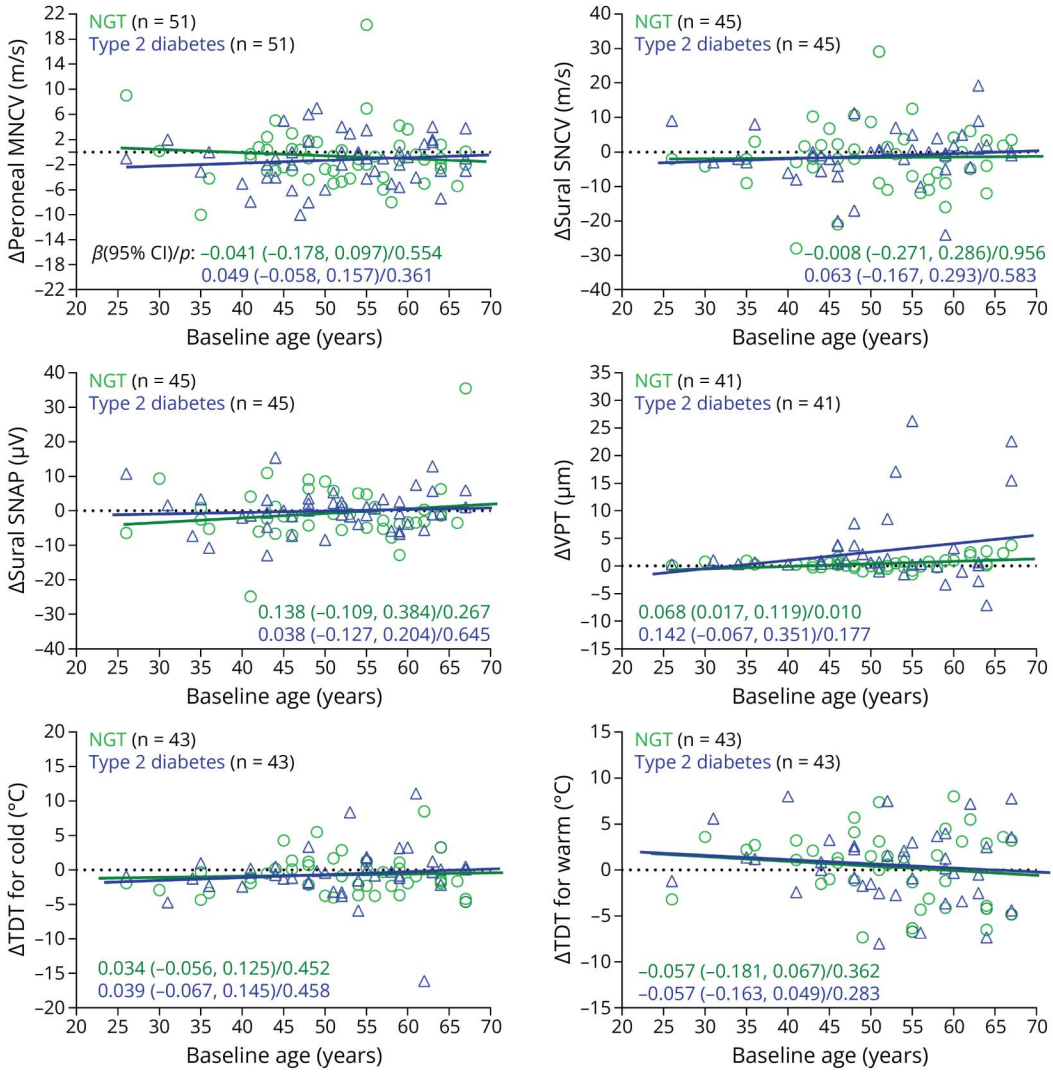
Demographic and Clinical Characteristics in Participants With Type 2 Diabetes at 10-Year Follow-Up

The demographic and clinical data of 141 participants with type 2 diabetes, assessed at baseline and 5-year and 10-year follow-ups, are summarized in eTable 3. After 10 years, height, diastolic blood pressure, total cholesterol, M-value, creatinine, hsCRP, and albuminuria decreased while triglycerides, HDL cholesterol, HbA1c, and fasting blood glucose increased (all $p < 0.05$). Smoking prevalence and LDL cholesterol increased after 5 years (both $p < 0.05$) and returned to baseline levels after 10 years. No differences between baseline and 10-year follow-up were observed for the remaining variables. Diabetes control levels shifted over time: at baseline, approximately 80% of participants had well-controlled (HbA1c <7%), 18% had fairly controlled (HbA1c 7%–9%), and 2% had poorly controlled (HbA1c >9%) diabetes. These proportions changed to roughly 63%, 33%, and 4% at 5 years and 52%, 41%, and 7% at 10 years.

Changes in Nerve Function in Participants With Type 2 Diabetes at 10-Year Follow-Up

The median values of peripheral nerve function indices and clinical scores and DSPN prevalence at baseline, after 5 years, and after 10 years in the group with type 2 diabetes are provided in Table 2. After 5 years, peroneal MNCV and sural SNAP decreased while VPT increased compared with

Figure 2 Individual Changes in Nerve Function After 5 Years in People With Normal Glucose Tolerance and Type 2 Diabetes in Relation to Baseline Age



Linear regression analyses with nerve function measures as the dependent variable and baseline age as the independent variable were used to determine the deviation from zero.

Table 2 Neurophysiologic Parameters and Clinical Scores of Individuals With Type 2 Diabetes With a 10-Year Follow-Up

	N	Baseline	5 Y	10 Y
Peroneal MNCV (m/s)	141	46.0 (43.0, 49.0)	44.0 (40.0, 46.0)[a]	42.0 (39.8, 44.1)[a,b]
Sural SNCV (m/s)	120	46.3 (41.1, 49.0)	44.0 (41.0, 48.0)	42.0 (37.3, 46.0)[a,b]
Sural SNAP (μV)	124	8.2 (5.3, 12.5)	7.3 (5.2, 10.3)[a]	6.4 (3.5, 9.4)[a,b]
VPT (μm)	118	0.83 (0.47, 1.73)	1.29 (0.82, 2.88)[a]	1.84 (0.93, 4.37)[a,b]
TDT for cold (°C)	129	29.4 (27.0, 30.3)	28.5 (26.6, 30.0)	28.0 (25.2, 29.6)[a,b]
TDT for warm (°C)	133	39.4 (36.7, 42.6)	39.8 (37.1, 43.0)	40.3 (37.6, 44.2)[a]
Neuropathy Symptom Score (NSS) (points)	128	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 5.0)[a,b]
Neuropathy Disability Score (NDS) (points)	126	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	2.0 (0.8, 4.0)[a,b]
DSPN (%)*	104	3.8	1.9	8.6
Subclinical DSPN (stage 1a)		3.8	1.9	3.8
Confirmed asymptomatic DSPN (stage 1b)		0.0	0.0	1.0
Confirmed DSPN (stage 2)		0.0	0.0	3.8

Abbreviations: MNCV = motor nerve conduction velocity; N = number of participants with prospective data for the corresponding variable; SNAP = sensory nerve action potential; SNCV = sensory nerve conduction velocity; TDT = thermal detection threshold; VPT = vibration perception threshold.
Data are % or median (first, third quartile).
[a] $p < 0.05$ vs baseline
[b] $p < 0.05$ vs NGT follow-up (Wilcoxon signed rank test and *McNemar test).

baseline (all $p < 0.05$). After 10 years, all peripheral nerve function indices and clinical scores worsened compared with baseline (all $p < 0.05$). In addition, all peripheral nerve tests, except warm TDTs, and both clinical neuropathy scores deteriorated from 5 to 10 years (all $p < 0.05$). The patterns of decline from baseline to 5 years were consistent to those from 5 to 10 years across all 6 parameters (Figure 3).

To determine whether older age was associated with a greater decline in nerve function in this larger group, 10-year changes in nerve function were plotted against baseline age. Linear regression analyses showed that older age was associated with increased VPT and improved sural SNAP (Figure 4) while changes in the other 4 parameters showed no age-related associations. Analysis of changes in sural SNAP and VPT from baseline to 5 years, as well as from 5 to 10 years, revealed an age association only in the baseline-to-5-year VPT change (eFigure 3).

Predicted vs Observed Prevalence of Abnormal NCV

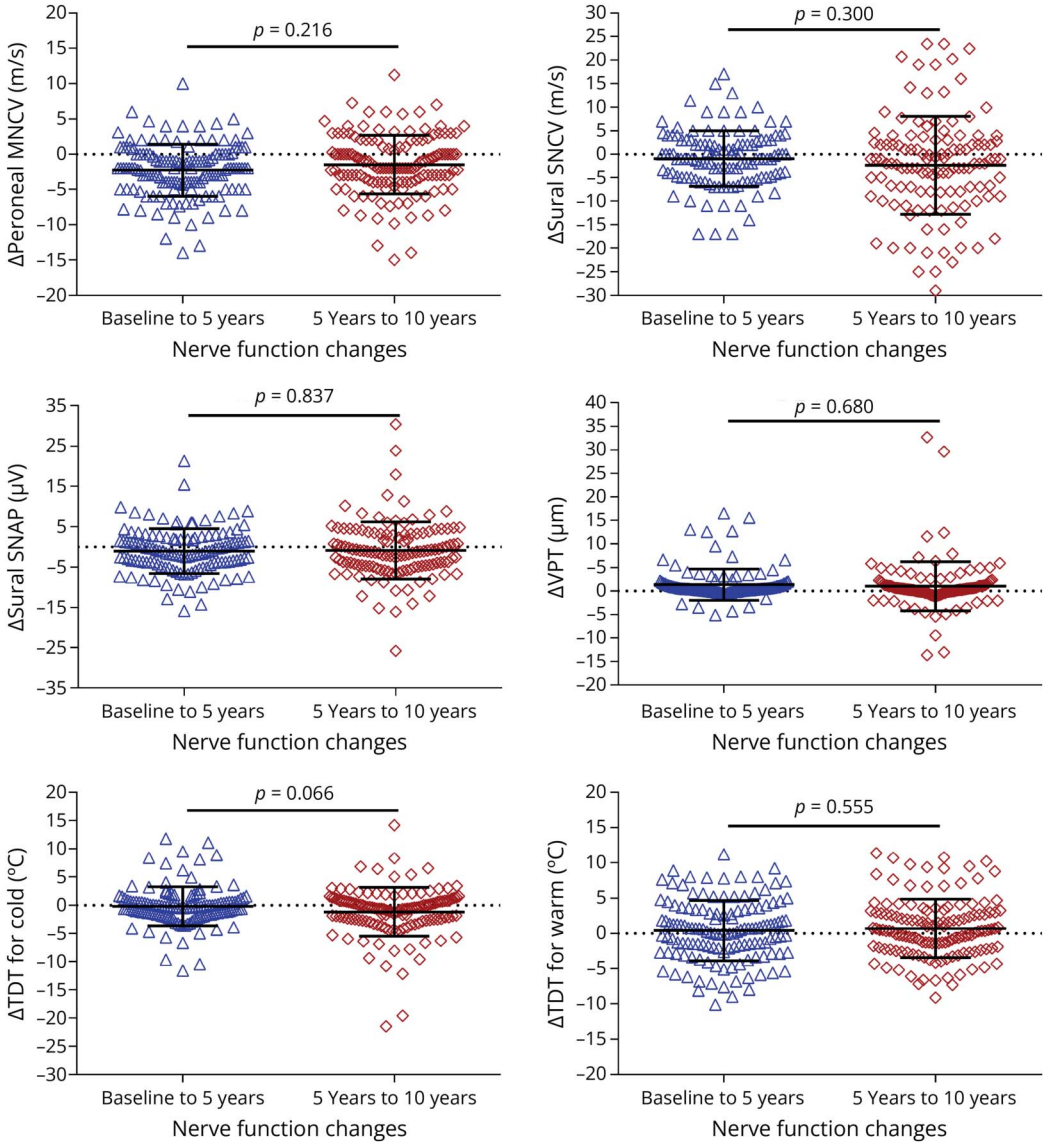
The median annual decline in peroneal MNCV and sural SNCV among individuals with NGT was 0.2 m/s and 0.4 m/s, respectively. The observed prevalence of abnormal peroneal MNCV and sural SNCV in the participants with type 2 diabetes at the 10-year follow-up closely aligned with the estimated prevalence based on natural median NCV deterioration rates (Table 3). Specifically, the observed prevalence was 14.2% for peroneal MNCV, compared with an estimated 12.8%, and 30.2% for sural SNCV, nearly identical to the estimated 31.0%. eAppendix 1 includes a tool for estimating individual risk and the anticipated onset of abnormal peroneal and sural nerve function, accounting for physiologic aging-related decline. The prediction tool showed an accuracy of 0.75 for peroneal MNCV and 0.85 for sural SNCV.

Discussion

This study demonstrates a parallel decline in nerve function after 5 years in individuals with NGT and those with recently diagnosed, well-controlled type 2 diabetes. In participants with type 2 diabetes, this decline persisted throughout the first decade after diagnosis, with no discernible difference between the initial and latter halves of this period. The prevalence of abnormal NCV at 10 years in the type 2 diabetes group was consistent with the expected prevalence based on the natural aging-related decline in nerve function applied to nerve function levels observed at baseline. We also developed a practical tool, validated in the 10-year follow-up cohort, to estimate the onset of incident nerve dysfunction, assuming that favorable glycemic control is maintained.

While poor glycemic control has been considered a major contributor to the onset of DSPN in type 2 diabetes, older age is also considered to be an independent risk factor.[5] However, clinical intervention studies targeting glycemic control and/or other cardiovascular risk factors have largely failed to prevent or significantly alter the course of DSPN in people with type 2 diabetes.[11] Most previous prospective studies on nerve function decline in type 2 diabetes did not include NGT

Figure 3 Individual Changes in Nerve Function in People With Type 2 Diabetes From Baseline to 5 Years and From 5 to 10 Years

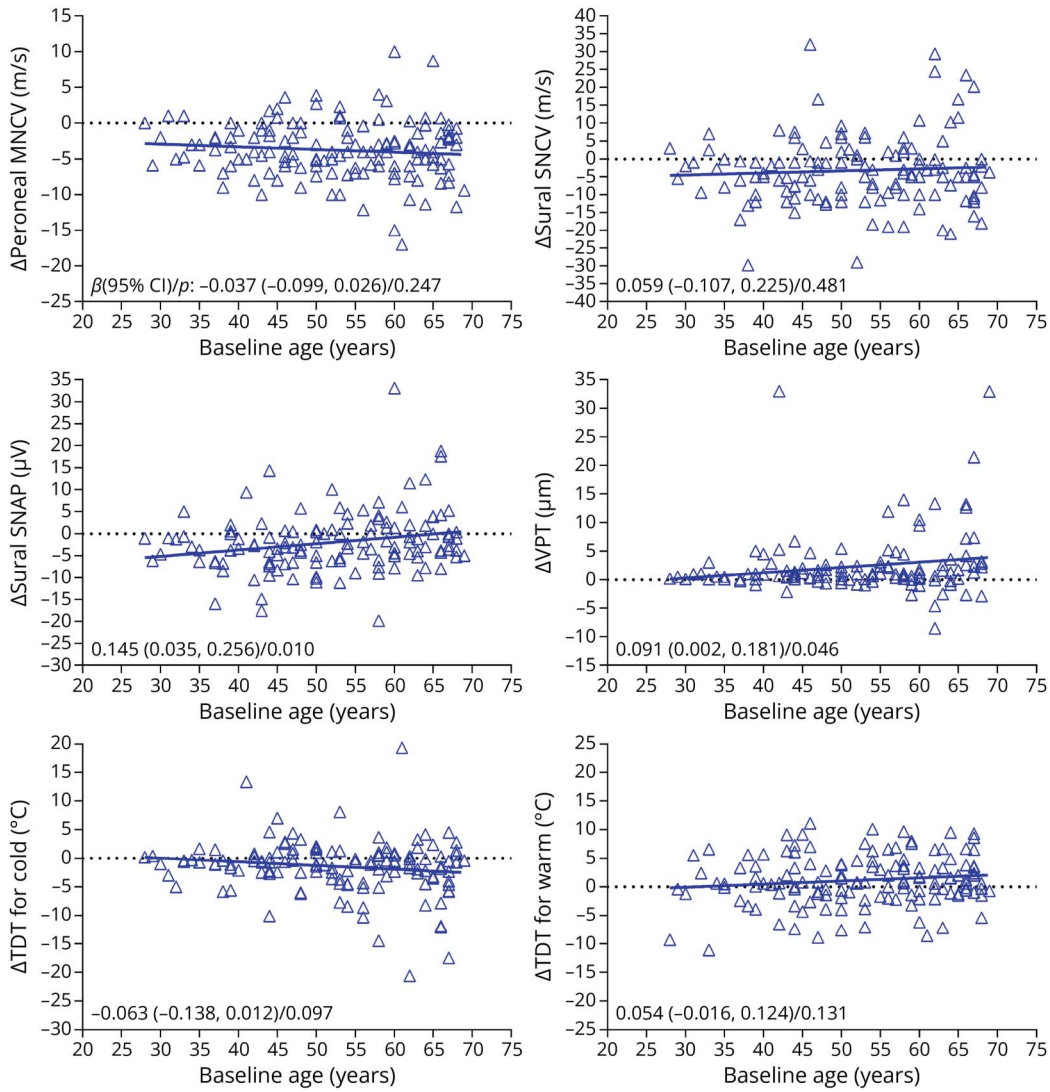


Bars are mean ± SD. Differences between the groups were assessed using the Wilcoxon signed rank test. BL = baseline, 5 years = 5-year follow-up, 10 years = 10-year follow-up.

controls. In a comparably designed study, a decline in peroneal and sural NCV over 10 years was observed in people with newly diagnosed type 2 diabetes, but not in the control group.[20] In contrast to our study, the diabetes group was characterized by poor glycemic control and the control group had a mean fasting glucose that would be considered impaired according to current ADA guidelines.[21] Moreover, their analysis did not account for repeated measures, and baseline and follow-up sample sizes differed.

In this study, no association between glycemic control and nerve function decline was found after 5 or 10 years. However, glycemic control was relatively stable, with well-controlled or fairly controlled diabetes observed in more than 90% of participants at both baseline and follow-ups. This suggests that the nerve function decline in well-controlled type 2 diabetes is primarily due to physiologic changes. While the course of nerve function deterioration and DSPN development cannot be directly compared between type 2 and type 1 diabetes, our previous findings suggest a similar pattern in individuals with type 1 diabetes. We showed, in a 24-year follow-up study in individuals newly diagnosed with type 1 diabetes, that among participants who maintained near-normoglycemia over 24 years, the decline in nerve function was comparable with that in individuals without diabetes.[22] In addition, none of the participants who maintained near-normoglycemia developed DSPN after 24 years while 64% of those with poor glycemic control did develop DSPN. Similar results were reported

Figure 4 Individual Changes in Nerve Function After 10 Years in People With Type 2 Diabetes in Relation to Baseline Age



Linear regression analyses with nerve function measures as the dependent variable and baseline age as the independent variable were used to determine the deviation from zero.

in a recent 3-decade follow-up study in individuals with childhood-onset type 1 diabetes.[23]

The results of this study suggest that nerve damage occurring during prediabetes and/or undiagnosed type 2 diabetes plays a key role in the manifestation and progression of DSPN once the disease becomes clinically manifest. This could explain why, unlike type 1 diabetes,[24-27] interventions aimed at improving glycemic control and other cardiovascular risk factors have not had a meaningful impact on neuropathy-related

Table 3 Observed and Estimated Prevalence of Abnormal NCV in Individuals With Type 2 Diabetes at 10-Year Follow-Up

Indices	N	Observed prevalence	Estimated prevalence[a]	*p* Value
Peroneal MNVC (%)	141	14.2	12.8	0.824
Sural SNCV (%)	125	30.2	31.0	1.000

Abbreviations: MNCV = motor nerve conduction velocity; SNCV = sensory nerve conduction velocity.
McNemar test.
[a] The estimated prevalence of abnormal NCV was determined by adjusting the baseline values for the corresponding aging-dependent median decline in nerve function over 10 years. The median per-year decline in NCV was calculated using the 5-year changes in individuals with normal glucose tolerance (0.2 m × s^{-1} × y^{-1} for peroneal MNCV and 0.4 m × s^{-1} × y^{-1} for sural SNCV).

outcomes in people with type 2 diabetes.[28-31] For example, in the ACCORD study, intensive glycemic control reduced the relative risk of incident DSPN by only 5%–9% in individuals with type 2 diabetes.[31] In the Steno-2 study, 7.8 years of intensified multifactorial risk intervention did not alter the prevalence of DSPN, as assessed by VPT, over 13 years.[30] Furthermore, at the 21-year follow-up of Steno-2, the hazard for all microvascular complications was decreased in the intensive-therapy group, except for peripheral neuropathy.[32]

In contrast to type 1 diabetes, where undetected hyperglycemia is typically brief, type 2 diabetes can remain undiagnosed for years, especially during asymptomatic stages.[33] This prolonged period of unmanaged hyperglycemia may contribute to the development of chronic diabetes-related complications, including DSPN.[34,35] The role of prediabetes in neuropathy development is increasingly being recognized, although studies have reported mixed results, likely due to varying diagnostic criteria for DSPN.[36] While several studies have not reported an increased DSPN prevalence in prediabetes, a comparison of continuous, objective nerve function measures might be more expedient to detect early signs of nerve damage, even before clinically manifest impairments are present. In the population-based MAASTRICHT study, hyperglycemia, including levels below the range typically found in people with diabetes, was consistently associated with peripheral nerve dysfunction as assessed by sum scores of nerve conduction indices,[37] supporting the hypothesis that prediabetes plays a role in early nerve damage.

Our findings have important implications for clinical practice and clinical trial design. They suggest that peripheral nerve dysfunction in well-controlled type 2 diabetes is primarily determined by nerve function levels at diagnosis and physiologic aging, provided that there is no further metabolic deterioration within the first decade after diagnosis. This may explain the difficulty in preventing the development or progression of nerve dysfunction after type 2 diabetes diagnosis. To improve or to restore nerve function, both previous nerve damage and the natural aging-related decline must be reversed—an outcome that is currently not achievable. Hence, early identification and intervention for individuals at high risk of type 2 diabetes or those with undiagnosed diabetes remain critical. Pathophysiology-based subphenotyping to identify individuals at high risk of developing type 2 diabetes[38] could be a promising strategy for targeted prevention.

This prospective study has certain strengths. First, the pairwise comparison of participants with NGT and recently diagnosed type 2 diabetes reduced confounding by major demographic variables. Second, we used comprehensive, gold standard methods to assess peripheral nerve function and DSPN. Third, the inclusion of a large 10-year follow-up cohort strengthens the findings. However, there are limitations, including the delayed recruitment of participants with NGT in the German Diabetes Study, which started approximately 8 years later than in individuals with diabetes. This resulted in a small group for the 5-year comparison and a lack of 10-year follow-up data for the NGT group. In addition, a subgroup of individuals with poorly controlled diabetes would have strengthened the outcomes of the study. Furthermore, the differences in examination procedures preclude a direct comparison with other studies. Finally, more measures of large compared with small nerve fiber function were included in the analysis. However, our previous findings from the diabetes cohort of the GDS indicated a parallel impairment of both nerve fiber types rather than predominant small fiber damage.[8]

In conclusion, our study highlights that the trajectory of nerve function deterioration in newly diagnosed, well-controlled type 2 diabetes is primarily shaped by nerve function levels at diabetes diagnosis and by aging-related physiologic changes, rather than by disease progression. These findings underscore the importance of early detection and intervention strategies in individuals at high risk of type 2 diabetes and those with undiagnosed diabetes.

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Author Contributions

A. Strom: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. K. Strassburger: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D. Ziegler: drafting/revision of the manuscript for content,

including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. G. Sipola: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Prystupa: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Wagner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Roden: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G.J. Bönhof: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data.

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