Journal of Diabetes and Its Complications 29 (2015) 998–1002

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

# High prevalence of diagnosed and undiagnosed polyneuropathy in subjects with and without diabetes participating in a nationwide educational initiative (PROTECT study)

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ARTICLE INFO

*Article history:*
Received 9 July 2015
Received in revised form 8 September 2015
Accepted 9 September 2015
Available online 14 September 2015

*Keywords:*
Polyneuropathy
Diagnosis
Screening
Foot care
Glycemic control
Peripheral arterial disease
PROTECT study

ABSTRACT

*Aims:* Since neuropathy screening may be underutilized in primary care practice, we conducted a nationwide educational initiative to determine the prevalence of diagnosed and previously undiagnosed polyneuropathy.
*Methods:* Among 1017 individuals participating in the initiative, 983 with complete data were analyzed, 359 of whom had no diabetes by history (ND), 80 had type 1 diabetes, and 544 had type 2 diabetes. Polyneuropathy was assessed by history and foot examination including pressure, temperature, and vibration perception and was classified as possible, probable, and severe. Foot pulses and HbA1c were determined in subsets of participants.
*Results:* Polyneuropathy was detected in 53.8% of ND, 43.8% of type 1, and 55.6% of type 2 diabetes subjects and was associated with higher age. In a subset of participants with polyneuropathy, the latter was declared as previously undiagnosed by 79.1% of ND, 35.7% of type 1, and 61.5% of type 2 diabetes participants. After adjustment for age and sex, prevalent polyneuropathy was associated with peripheral arterial disease.
*Conclusions:* More than half of subjects with and without diabetes participating in an educational initiative had polyneuropathy which was reported as previously undiagnosed by two thirds. Effective strategies to avoid underdiagnosis of neuropathy and to improve preventive foot care should be implemented.


## 1. Introduction

Polyneuropathy is encountered in about one third of all diabetic patients (Ziegler, Papanas, Vinik, & Shaw, 2014) and predicts cardiovascular morbidity (Brownrigg et al., 2014) and mortality (Calles-Escandón et al., 2010). Painful neuropathy is observed in 13%–26% of individuals with diabetes and exerts a substantial impact on the quality of life (Ziegler, Papanas, et al., 2014). Bed-side screening instruments to detect clinically manifest polyneuropathy such as the tuning fork to determine the vibration perception threshold (VPT), 10 g monofilament to assess touch/pressure perception, and tools to examine thermal sensation have been shown to predict diabetic foot ulcers (Abbott et al., 2002; Crawford et al., 2011). Consequently, the American Diabetes Association recommends that all patients should be screened for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter, using simple clinical tests, such as a 10-g monofilament (American Diabetes Association, 2015a). Regrettably, neuropathy screening is underutilized in primary care practice (Kirkman, Williams, Caffrey, & Marrero, 2002; O'Brien et al., 2003). In a recent survey from Spain, diabetic foot screening (inspection, monofilament testing, and palpation of peripheral pulses) was performed in 37% of diabetic patients in primary care (Alonso-Fernández et al., 2014). Moreover, the clinical impact of polyneuropathy is still being underestimated by both physicians and patients. In a large US nation-wide survey, physicians reported a neuropathy prevalence of 18%, but subsequent monofilament testing detected a prevalence of 37% in patients with type 2 diabetes. Moreover, physicians prospectively identified only 31% and 66% of patients with mild/moderate and severe neuropathy, respectively (Herman & Kennedy, 2005).

Conflict of interest: DZ, RL, KHR, KR, and OS are advisory board members of the National Education Initiative and received honoraria for speaking activities from Wörwag Pharma.

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http://dx.doi.org/10.1016/j.jdiacomp.2015.09.008
1056-8727/

Furthermore, diabetic subjects are frequently unaware of having neuropathy. Among diabetic patients with neuropathic symptoms from five rural Arkansas counties who attended a diabetes education program, 79% had not been diagnosed with polyneuropathy (Wang, Balamurugan, Biddle, & Rollins, 2011). In the German population based KORA F4 study, 77% of elderly subjects with known diabetes and polyneuropathy were unaware of having the neuropathy (Bongaerts et al., 2013). In the Australian community-based Fremantle Diabetes Study Phase II among participants with diabetes who considered their feet to be normal, 67.9% had sensory polyneuropathy, suggesting that self-assessment of diabetes-related foot problems by patients is unreliable (Baba, Foley, Davis, & Davis, 2014).

Thus, underdiagnosis of diabetic polyneuropathy could have an impact on the development of diabetic foot ulcers and even amputations. The rates of undiagnosed neuropathy among individuals without diabetes are unknown. We conducted a nationwide educational initiative to determine the prevalence of diagnosed and previously undiagnosed polyneuropathy in individuals with and without diabetes.

## 2. Subjects, materials and methods

### 2.1. Study population

This nationwide educational initiative (Nationale Aufklärungsinitiative [NAI]) "Diabetes! Do you listen to your feet?" (PROTECT study) was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Heinrich Heine University, Düsseldorf, Germany. All participants provided a written informed consent. From May 2013 through November 2014, 26 events with promotional stands have been performed nationwide in Germany, 13 of which were organized in shopping centers and 13 in diabetes and health care fairs. Visitors attending the promotional stand were invited to test their foot sensation by walking over a barefoot course with four different floorings. Furthermore, educational measures included lectures and consultations with experts about diabetes and diabetic neuropathy given by diabetologists at the promotional stand, consultations by the podologists during and after the foot examination, broad public relations activities by print, online, and broadcasting media, news services, editorial media reports, and distribution of information material at the promotional stand (newsletter, brochures, guides, etc.), regional letters of announcement to physicians and pharmacists, and nationwide information letters to (around 50,000) general practitioners and diabetologists. Each year since 2013, a press conference for the specialist and end-user media was held on the occasion of the annual congress of the German Diabetes Association. The NAI website (www.hoerensieaufihrefuesse.de) is the central online platform for all activities and information provided by NAI. As an added value, it features a video consultation by five diabetologist and neurologist experts on topics related to diabetes and neuropathy.

### 2.2. Methods

Study participants with or without known diabetes underwent a foot examination and completed a questionnaire including age, sex, history of type 1 or type 2 diabetes and answered the following questions: 1) "Have you ever been diagnosed with neuropathy?", 2) "Are you currently being treated by a physician due to neuropathy?"

Foot examination was carried out by certified podologists in quiet ambience in a mobile cube (9 $m^2$)with a sliding door closed and included bilateral assessment of pressure, temperature, and vibration sensation which were tested two times on each site and foot. The subject was asked to close his eyes during each test. Pressure perception was determined twice on the plantar aspect of each second metatarsal head using the 10 g monofilament (Rehaforum Medical, Elmshorn, Germany) avoiding callous skin. Subjects indicated when a touch occurred which was classified as normal and as abnormal if the monofilament was not felt (Viswanathan, Snehalatha, Seena, & Ramachandran, 2002; Ziegler, Keller, Maier, & Pannek, 2014). Pressure perception was defined as abnormal if the subject did not feel the monofilament twice on both sides or twice on one side and once on the other. Temperature perception was carried out twice on each dorsum of the foot using the tip therm® device (tip therm, Brüggen, Germany). The examiner placed each of the two flat surfaces of the device at irregular intervals avoiding callous skin and asks whether it feels cold or not so cold (Viswanathan et al., 2002). Thermal perception was defined as abnormal if the subject did not answer correctly twice on both sides or twice on one side and once on the other. Vibration perception threshold (VPT) was determined on the dorsum of the interphalangeal joint of the hallux and medial malleolus using the Rydel–Seiffer tuning fork (Arno Barthelmes Zella-Mehlis, Zella-Mehlis, Germany) as previously described (Martina, van Koningsveld, Schmitz, van der Meché, & van Doorn, 1998). The readings of two repeated tests were averaged and defined as VPT for each of the two sites of examination. The age- and sex-dependent limits of normal previously reported by Martina et al. (1998) defined at the 5th percentile of healthy subjects were used. VPT was defined as abnormal if the mean of two sides on the dorsum of the interphalangeal joint of the hallux and/or medial malleolus was below the 5th percentile of healthy subjects. Distal sensory polyneuropathy (DSPN) was defined as possible, probable, and severe if 1 out of 3, 2 out of 3, and 3 out of 3 tests (pressure, temperature, vibration perception), respectively, were abnormal.

Pedal pulses of the dorsalis pedis and posterior tibial arteries were examined in a subset of 596 participants. Foot pulses were classified as indicating peripheral arterial disease (PAD) if at least two out of the four pulses were not palpable.

HbA1c was measured using a point of care DCA Vantage Analysis System (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) in a subset of 189 participants. According to the American Diabetes Association (ADA) criteria (American Diabetes Association, 2015b), diabetes was defined as HbA1c ≥ 6.5% and prediabetes as HbA1c ≥ 5.7% to <6.5%, while HbA1c <5.7% was considered normal.

### 2.3. Statistical analysis

Continuous data were expressed as mean ± SD. Categorical data were given as absolute or relative frequencies with 95% CI and were analyzed by Fisher's exact test. For normally distributed data, parametric tests (t-test or Pearson product–moment correlation) were applied; otherwise, nonparametric tests (Mann–Whitney U test or Spearman rank correlation) were used. To determine associations between two variables, univariate correlations and multiple linear regression analyses were performed. The level of significance was set at $\alpha = 0.05$.

## 3. Results

Among 1017 individuals participating in the initiative, 6 had no information on diabetes and 28 had missing data for pressure, temperature or vibration perception, leaving 983 participants with a complete data set for analysis, 359 of whom had no diabetes by history (ND), 80 had type 1 diabetes, and 544 had type 2 diabetes. The clinical data and prevalence of abnormal sensory tests and DSPN in the three groups studied are given in Table 1. Men were more frequent in the group with type 2 diabetes than in the group without diabetes history ($P < 0.05$). Type 1 diabetic subjects were younger than those with type 2 diabetes and without diabetes history ($P < 0.05$). HbA1c was higher in the groups with diabetes than in the group without diabetes history ($P < 0.05$). No significant differences between the groups were noted for the remaining