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Polyneuropathy is inadequately treated despite increasing symptom intensity in individuals with and without diabetes (PROTECT follow-up study)

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ABSTRACT

Aims/Introduction: Despite its major clinical impact, distal symmetric polyneuropathy remains frequently undiagnosed and undertreated in clinical practice. We previously reported in the PROTECT Study that 70% of type 2 diabetes patients with distal symmetric polyneuropathy were unaware of having the latter condition.

Materials and Methods: In the present follow up after 2.5 ± 0.7 years, 122 and 85 participants with and without type 2 diabetes, respectively, completed questionnaires to obtain information about the further course of disease and its management.

Results: At follow up, 49 and 48% of the respondents with type 2 diabetes and without diabetes, respectively, reported that the intensity of paresthesia or numbness in the feet increased, whereas for burning and pain in the feet the corresponding percentages were 56 and 61%. However, 33 and 40% of the respondents with type 2 diabetes and without diabetes, respectively, reporting neuropathic symptoms at follow up did not receive any pharmacotherapy. Pharmacotherapy of neuropathic symptoms at follow up among participants with type 2 diabetes and without diabetes included mainly World Health Organization Step 1 analgesics (17% each; excluding acetylsalicylic acid), pregabalin/gabapentin (20 and 12%), vitamin B complex (13 and 22%), benfotiamine (13 and 2%), opioids (7 and 12%), antidepressants (4 and 5%) and α-lipoic acid (4 and 2%).

Conclusions: These findings point to insufficient care, inadequate treatment adherence or limited efficacy of treatments in patients with polyneuropathy, suggesting that effective measures should be implemented to correct these healthcare deficits.

INTRODUCTION

Chronic distal sensorimotor polyneuropathy (DSPN) affects approximately one-third of patients with diabetes, but remains frequently undiagnosed and often undertreated in clinical practice, despite its major clinical impact[1–3]. It has been suggested to define DSPN in clinical practice as the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes[4]. Pain associated with DSPN exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life[1]. Chronic painful diabetic polyneuropathy (PDPN) is encountered in 13–26% of patients with diabetes[1], but in up to half of them DSPN might be asymptomatic, exposing patients to an increased risk for injuries to their insensate feet[4,5]. Regrettably, in a survey from Spain, diabetic foot screening was carried out in just 37% of patients with diabetes in primary care[6]. Furthermore, the clinical impact of DSPN is still being underestimated by both physicians and patients. In a large USA nationwide survey, physicians reported a neuropathy prevalence of 18%, but subsequent monofilament testing detected a prevalence of 37% in type 2 diabetes patients[7]. Several studies suggest that both people with diabetes and their

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treating physicians are frequently unaware of having neuropathy[8–11] or diabetic foot disease[12,13].

In the PROTECT Study, we reported that painful and painless DSPN remained undiagnosed in 57 and 82% of type 2 diabetes patients, respectively[2]. In the present mean follow up after 2.5 years, we sought to obtain information about the further course of the disease and its management.

METHODS

Study population

The present study was a follow up of the nationwide educational initiative (Nationale Aufklärungsinitiative) "Diabetes! Do you listen to your feet?" (PROTECT study) during which 1,850 participants with or without diabetes had undergone a foot examination by certified podologists as previously described.[2] DSPN was assumed if pressure, temperature and/or vibration perception were abnormal.[2] This follow up was carried out 2.5 ± 0.7 years after the baseline examination using a standardized questionnaire that was sent out to the participants after obtaining their consent. Among others, participants were asked if they have non-painful neuropathic symptoms, such as tingling or numbness, and painful neuropathic symptoms, such as burning or pain, and as to whether these symptoms were now stronger, weaker or unchanged when compared with baseline. Furthermore, participants had to tick a box if they received any treatment against nerve damage (neuropathy) or complaints in the feet (tingling, burning, pain and/or numbness). The following treatment options including widely known trade names were offered (multiple answers possible): acetylsalicylic acid, ibuprofen, diclofenac, paracetamol, metamizol, pregabalin, gabapentin, other anti-epileptics (such as carbamazepine), duloxetine, tricyclic antidepressants (such as amitriptyline), weak opioids (tramadol, tilidine), strong opioids (tapentadol, oxycodone, fentanyl), α-lipoic acid, benfotiamine, vitamin B complex, other preparations, capsaicin cream or patch, electrical therapy, acupuncture and miscellaneous. Respondents included 85 participants without a history of diabetes and 122 participants with type 2 diabetes, whereas 15 respondents with type 1 diabetes were excluded because of the small sample size.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation. Categorical data were given as absolute or relative frequencies and were analyzed by Fisher's exact test. For normally distributed data, the parametric *t*-test was used, otherwise, the non-parametric Mann–Whitney *U*-test was applied. Longitudinal data were analyzed by paired *t*-test. The level of significance was set at $\alpha = 0.05$.

RESULTS

The demographic and clinical data of the respondents at baseline are listed in Table 1. The group with type 2 diabetes included more men than women, was older, and had higher body mass index and weight ($P < 0.05$), whereas height did not differ between the groups.

The results for questions about the management of DSPN at follow up are shown in Table 2. Respondents with type 2 diabetes compared with those without diabetes more frequently had DSPN treatment accompanied by a physician, more frequently carried out daily foot inspection and more frequently had their feet examined by a physician ($P < 0.05$). No differences between the groups were noted for the remaining questions.

Table 3 shows the percentages of respondents with neuropathic symptoms in the feet at baseline and follow up, and the course of these symptoms from baseline to follow up. Although the percentages of respondents with paresthesia and/or numbness did not change from baseline to follow up, those with burning and numbness decreased in the group without diabetes ($P < 0.05$), but not in the group with type 2 diabetes. The majority of respondents reported that neuropathic symptoms became more severe (48–61%). Among those who did not have neuropathic symptoms at baseline, 26–54% reported at follow up that they had developed symptoms. Among respondents with neuropathic symptoms at baseline, 9–23%

Table 1 | Demographic and clinical data of the respondents at baseline

	No diabetes	Type 2 diabetes
n	85	122
Sex (% male)	40.0	56.6*
Age (years)	71.4 ± 11.7	74.5 ± 7.9*
BMI (kg/m^2)	26.3 ± 4.7	29.0 ± 4.9*
Weight (kg)	76.0 ± 17.0	83.2 ± 15.6*
Height (cm)	170 ± 10	169 ± 9
Diagnosis of DSPN (%)	51.8	52.1
Time to follow up (years)	2.47 ± 0.66	2.50 ± 0.68

Values are mean ± standard deviation or percentages. *$P < 0.05$ versus no diabetes. DSPN, distal symmetric polyneuropathy.

Table 2 | Management of distal symmetric polyneuropathy at follow up

	No diabetes ($n = 41$)	Type 2 diabetes ($n = 68$)
Treatment against nerve damage or neuropathic symptoms in the feet (%)	51.2	63.2
Treatment accompanied by physician (%)	60.0	86.5*
No pharmacotherapy of neuropathic symptoms (%)	40.0	32.7
No pharmacotherapy of neuropathic pain (%)	38.9	22.2
Daily foot inspection by respondent (%)	30.0	51.4*
Regular foot examination by physician (%)	10.0	38.6*

*$P < 0.05$ versus no diabetes.

Table 3 | Percentages of respondents with neuropathic symptoms in the feet at baseline and follow up, and their course from baseline to follow up

	No diabetes (n = 85)		Type 2 diabetes (n = 119)	
	Baseline (%)	Follow up (%)	Baseline (%)	Follow up (%)
Paresthesia/numbness	83.5	75.3	78.2	82.4
Stronger		56.3		51.5
Unchanged	–	39.1	–	40.4
Weaker	–	3.1	–	2.0
Resolved	–	17.2	–	9.1
Newly developed	–	28.6	–	53.8
Burning/pain	79.8	64.3*	68.1	60.5
Stronger	–	48.4	–	53.7
Unchanged	–	46.8	–	45.1
Weaker	–	0	–	0
Resolved	–	22.6	–	14.6
Newly developed	–	35.3	–	26.3

*$P < 0.05$ versus baseline.

reported at follow up that they no longer had symptoms. None of the respondents reported improvement of burning or pain, whereas 2–3% reported less paresthesia and/or numbness at follow up.

Table 4 shows the percentages of respondents receiving treatment against nerve damage (neuropathy) or symptoms in the feet classified by pathogenesis-oriented and other treatments, as well as analgesic pharmacotherapy. The three most frequent therapies (except for acetylsalicylic acid) in the group without a history of diabetes were vitamin B complex, non-steroidal anti-inflammatory drugs and $\alpha_2\delta$ ligands (pregabalin or gabapentin), whereas in the group with type 2 diabetes, the corresponding ranking included $\alpha_2\delta$ ligands, miscellaneous treatments, as well as vitamin B complex and benfotiamine. Treatment with World Health Organization Step 1 analgesics (except for acetylsalicylic acid) was reported by 17.4 and 17.1% of respondents with type 2 diabetes and without diabetes, and treatment with opioids by 7.2 and 12.2%, respectively.

DISCUSSION

The results of this 2.5-year follow up of the nationwide educational initiative "Diabetes! Do you listen to your feet?" unveiled that approximately half of the respondents with neuropathic symptoms in the feet at baseline reported an increased symptom intensity. However, more than one-third did not receive any pharmacotherapy, despite the fact that they reported neuropathic symptoms at follow up. Furthermore, 17% of the respondents reported to receive treatment with World Health Organization Step 1 analgesics (apart from acetylsalicylic acid) particularly including NSAIDs, which are not recommended for the treatment of neuropathic pain by international guidelines[4]. In conclusion, these findings suggest insufficient care, possible treatment non-adherence or limited efficacy of treatments in patients with DSPN.

Table 4 | Percentages of respondents receiving treatment against nerve damage (neuropathy) or symptoms in the feet classified by pathogenesis-oriented or other treatment and analgesic pharmacotherapy

	No diabetes (n = 41)	Type 2 diabetes (n = 70)
Pathogenetic/other treatment (%)		
Vitamin B complex	22.0	13.0
Benfotiamine	2.4	13.0
α-Lipoic acid	2.4	4.3
Other drugs	4.9	10.1
Electrical therapy	4.9	4.3
Acupuncture	0	1.4
Miscellaneous	9.8	17.4
Analgesic pharmacotherapy (%)		
Non-steroidal anti-inflammatory drugs	17.1	7.2
Acetylsalicylic acid	9.8	22.1
Paracetamol	0	1.4
Metamizol	4.9	10.1
$\alpha_2\delta$ Ligands (pregabalin, gabapentin)	12.2	20.3
Antidepressants	4.9	4.3
Weak opioids (tramadol, tilidine)	7.3	5.8
Strong opioids	7.3	2.9
Capsaicin	0	1.4

Evidence has emerged suggesting that DSPN and PDPN are not being adequately managed in clinical practice. The present results with respect to pharmacotherapy of PDPN are in line with previous reports by others and ourselves[3,14,15] showing that $\alpha_2\delta$ subunit calcium channel modulators are most frequently used, antidepressants are underused, and NSAIDs are relatively frequently used despite the lack of guideline

recommendations. In a prospective study from the UK, 35% of diabetes patients had never received treatment for their neuropathic pain, despite 96% reporting pain to their physician. Analgesic pharmacotherapy included antidepressants (44%), anticonvulsants (17%), opiates (39%) and complementary therapies (30%), but neuropathic pain resolved completely over a period of 5 years only in a minority (23%)[14]. In a retrospective survey of USA health insurance claims including 12,074 patients with PDPN, two thirds were initiated with an anticonvulsant (gabapentin 45.0%, pregabalin 21.6%), but just 5.2% with duloxetine. Patients commonly received less than the recommended dose of the prescribed medication, and adherence was suboptimal for all pharmacotherapies. Within 3 months of initiation, up to 50% of patients had discontinued their initial treatment. This indicates low treatment satisfaction and/or poor tolerability[15]. The frequent use of pregabalin in PDPN contrasts with a recent systematic review reporting that >50% (8/15) of the trials failed to show superiority over a placebo, suggesting a low strength of evidence for this agent in this condition[16]. Furthermore, the duration of analgesic pharmacotherapy in clinical trials usually did not exceed 12 weeks, whereas in clinical practice these drugs are frequently used for considerably longer periods. In the population-based KORA F4 survey, we found that just 38% of the participants with chronic PDPN received analgesic pharmacotherapy, predominantly NSAIDs (20%) and opioids (12%), whereas antidepressants and anticonvulsants were relatively underused[3].

We add to the current knowledge that despite increasing symptom or pain intensity, analgesic drugs, such as antidepressants, and pathogenesis-oriented treatments for diabetic neuropathy with proven efficacy remain underused[17,18], particularly the anti-oxidant, α-lipoic acid, which is recommended for diabetic neuropathy by systematic reviews[19,20]. Whereas the thiamine derivative and advanced glycated end-product inhibitor, benfotiamine[17,18] was used more often. Furthermore, 22 or 33% of the respondents with type 2 diabetes, and 39 or 40% of those without a history of diabetes received no pharmacotherapy for neuropathic pain or symptoms, respectively. Of note, compared with respondents with type 2 diabetes among those without a history of diabetes, treatment was less frequently accompanied by a physician, and the feet were less frequently self-inspected and examined by a physician. Overall, these data point to inadequate care and drug allocation for patients with DSPN. Of particular importance, evidence-based guidelines for physicians and patients are insufficiently, if at all, implemented in daily patient care.

One reason for limited efficacy of available pharmacotherapies is obviously their frequent underdosing. In a rural area in South Carolina, subtherapeutic doses of analgesic compounds were used by >50% of the patients, with gabapentin being the most frequently used drug (65%). Altogether, >95% of treated patients did not receive optimal therapy according to the guidelines of the American Academy of Neurology[21]. In a 6-month prospective study including 1,523 participants with diabetes in whom treatment of PDPN was initiated with or changed to duloxetine, pregabalin or gabapentin, we found that the median daily dose over a period of 6 months was low for pregabalin (174 mg) and gabapentin (728 mg), whereas for duloxetine (54 mg) it was much closer to the recommended therapeutic dose. Thus, in primary care, particularly $\alpha_2\delta$ ligands are being frequently underdosed in patients with PDPN. This could be due to a prolonged titration phase as compared with duloxetine, which might contribute to limited efficacy[22].

Other factors that could contribute to inadequate management of PDPN include differences between physician and patient perceptions of the condition. In a study from five countries in Southeast Asia, physicians and patients had different views about the impact of PDPN. Although physicians believed that the main impact is on quality of life, patients believed that the impact was greater on sleep, anxiety, depression and work. For physicians, diagnosis and treatment of PDPN had low priority reflected by a low incidence of screening and lack of awareness of PDPN[23]. The physician–patient dialogue is essential to optimize patient outcomes. Therefore, it has been emphasized that to improve communication it would be important to develop new strategies, including education of both groups[23]. In our previous prospective study, the majority of patients with painful DSPN identified general activity and walking ability as the most important aspects for which they expect improvement from neuropathic pain treatment[24].

A major obstacle in establishing adequate management of diabetic neuropathy is the lack of awareness of the condition by both physicians and patients. Among diabetes patients from rural Arkansas who presented with neuropathic symptoms and attended a diabetes education program, 79% had not been diagnosed with DSPN[9]. In the KORA F4 survey, 77% of participants with diabetes and DSPN were unaware of having the disorder, and approximately one-quarter of the participants with known diabetes had never undergone a foot examination[8]. In a survey including 1,082 participants with type 2 diabetes attending two national diabetes centers in Qatar, 82% of patients with PDPN had not previously been diagnosed or treated for this condition[25]. In a study from Japan, physicians were aware of PDPN in just 36% of patients with the disorder[11]. A study from Romania showed that half of the participants with diabetes in whom a specific questionnaire indicated the presence of DSPN were unaware of having the condition[26], and a delay between the onset of neuropathic symptoms and seeking physician intervention was associated with an increased risk of foot ulcers[27]. Furthermore, the vast majority of patients with diabetes are unlikely to have foot examinations in their primary medical care[28]. In a study from India, the awareness of foot care among people with diabetes was low among those attending primary, secondary and tertiary levels of healthcare, and just 12.5% had received previous foot care advice from healthcare professionals[12]. In a regional hospital in Durban, South Africa, just 22% of participants reported having examined their feet, and only when they

experienced a problem[13]. Among participants from the Australian community-based Fremantle Diabetes Study Phase II who had diabetes and considered their feet to be normal, 67.9% had DSPN, suggesting that self-assessment of diabetes-related foot problems by patients is unreliable[10]. Thus, underdiagnosis and a lack of awareness of diabetic polyneuropathy could have an adverse impact on the development of diabetic foot ulcers and even amputations. Thus, teaching and training of physicians and patients about diabetic neuropathy remains completely unsatisfactory and disappointing. One reason could be that the "organ" foot is loaded with shame from the patient side and perceived as repulsive from the medical care side.

Inadequate attention to diabetic foot prevention practice and insufficient adherence to clinical guidelines should trigger new preventive strategies. It has been suggested that self-perceived foot health should be assessed in conjunction with foot examination findings, and that intensive education and monitoring might be necessary for those who consider their feet to be normal, but who have precursors of serious foot pathology[28]. Indeed, a simple, low-cost educational intervention over a period of 6 months resulted in an increase in the performance of proper foot examination from 14 to 62%[28]. More recently, it has been proposed that a paradigm shift from stratified healthcare toward personalized medicine is required to prevent diabetic foot ulcers. Such programs could be cost-effective, as a single episode of ulceration that is not prevented causes medical costs of approximately €10,000.[29] In patients without diabetes, similarly structured programs are completely missing, possibly because amputations are less common than in those with diabetes. At the primary healthcare level, professional sensitivity toward neuromuscular disorders is generally low, and many patients with neuropathic foot problems commonly turn to orthopedic surgeons rather than to adequate diabetes and neurological care.

The present study had several limitations. First, selection bias cannot be avoided due to the study setting and recall bias. Second, only a small proportion of participants from the baseline assessment completed the follow-up questionnaire, and no data on diabetes treatment and glycemic control were collected. Third, as this survey was primarily an educational campaign carried out in public settings, definitive diagnostic studies to confirm DSPN could not be carried out, and the causes of DSPN other than diabetes, such as vitamin B_{12} deficiency, alcohol abuse, monoclonal gammopathy, hypothyroidism, inflammation and drugs, as well as renal, hepatic, infectious, autoimmune or neoplastic disorders, could not be verified.

In conclusion, the results of this PROTECT Study follow up show that the intensity of neuropathic symptoms in the feet increased over a period of 2.5 years in approximately half of the respondent patients, yet more than one-third did not receive any pharmacotherapy for these symptoms. Furthermore, 17% of the respondents were reported to receive treatment with World Health Organization Step 1 analgesics (except for acetylsalicylic acid), particularly NSAIDs, which are not recommended for the treatment of neuropathic pain by evidence-based guidelines[4,30], suggesting insufficient care, inadequate treatment adherence or limited effectiveness of treatments in patients with DSPN. Thus, there is an unmet need to shift the current clinical practice of treating DSPN toward an evidence-based guideline-recommended approach. Future educational programs for people with diabetes and their physicians should address the gaps arising from underestimating DSPN in diagnosis and treatment in primary care, as well as inadequate implementation and adherence to clinical guidelines.

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DISCLOSURE

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