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ORIGINAL ARTICLE

Ambulatory screening of diabetic neuropathy and predictors of its severity in outpatient settings

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Abstract
Introduction Diabetic neuropathy is one of the most common causes of chronic neuropathic symptomatology and the most disabling and difficult-to-treat diabetic microangiopathic complication. The neuropathies associated with diabetes are typically classified into generalized, focal and multifocal varieties. There exists a scarcity of literature studying the correlation of different patient- and disease-related variables with severity of neuropathy.
Objectives This study aims to delineate the prevalence of diabetic neuropathy in type 2 diabetes, describe its characteristics and find out predictors of its severity.
Material and methods Eight hundred consecutive diabetic patients presenting to outpatient department (OPD) of Khan Research Labs (KRL) General Hospital and Centre for Diabetes and Liver diseases, Islamabad, during March–June, 2015 were made to complete a self-administered questionnaire (Michigan Neuropathy Screening Instrument—MNSI) and underwent a thorough physical examination according to MNSI protocols. A score of >2 was considered to be diagnostic for DPN. Patient and disease variables were noted. MNSI score was used as an index of severity of diabetic peripheral neuropathy (DPN). Correlation of several patient- and disease-related variables with the severity of DPN was determined using multivariate regression.
Results Out of a total 800 patients screened, 90 (11.25%) were found to have diabetic neuropathy. Of these 90, 45.5% were males, the median age was 54.47 ± 10.87 years and the median duration of diabetes was 11.12 ± 9.8 years. The most common symptom was found to be numbness (63.6%) followed by generalized body weakness (61.5%). The common findings on physical examination were dry skin/callus (38.7%) and deformities (14.7%). Duration of diabetes was found to be the strongest predictor for development and severity of diabetic neuropathy followed by glycemic controls (HbA1c values) and age.
Conclusion Duration of diabetes rather than diabetic controls predicts better the development and severity of diabetic neuropathy indicating a failure of intensive treatment to avert such complications.

Keywords Diabetes · Neuropathy · Screening

Introduction

In adults, symptoms of chronic neurological disorders are one of the most common reasons for physician visits [1]. Evaluation of sensory symptoms is one of the five most common reasons to visit to a neurologist. The prevalence of neuropathy in general population is 2.4% and increases to 8% in those older than 55 years [2, 3].

Diabetes mellitus is a global health issue affecting people of all age groups with prevalence gradually increasing to epidemic frequency [4]. This increase marks a parallel increment in the incidence of its micro- and macroangiopathic complications and the economic burden posed by these. Of these complications, diabetic neuropathy tends to be the most disabling and is an important therapeutic challenge for diabetologists and primary care physicians [5].

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Diabetes is one of the most common causes of peripheral neuropathy. Neuropathic prevalence in diabetes is 8% at the time of diagnosis [6, 7] and increases up to 66% with increased disease duration.

Chronic hyperglycemia-induced vascular and metabolic derangements are postulated to be the cornerstone for the pathogenesis of typical distal sensorimotor diabetic polyneuropathy, while intercurrent, painful neuropathy involving small fibers constitutes the chronic idiopathic axonal polyneuropathy (CIAP). Approximately one-third of the total patients with diabetes mellitus are thought to develop diabetic sensorimotor polyneuropathy and its subsequent complications [8]. Previously published literature reports chronic hyperglycemia to account for only a third of the total variance in severity of microangiopathic diabetic complications [9]. Impairment of lower-extremity sensations in addition to pain results in significant balance and movement disorders in a sizeable diabetic population. Neuropathy can predate the development of overt hyperglycemia or can occur at any point over the dysglycemia continuum.

Hyperglycemia, age, duration of diabetes, tobacco use, dyslipidemia, hypertension (especially diastolic), increased height, presence of cardiovascular disease (CVD), presence of severe ketoacidosis and presence of microalbuminuria (indicating early renal dysfunction) [10–12] are thought to be independent predictors for development of diabetic neuropathy, but there appears to be scarcity of literature studying the correlation of these factors to severity of diabetic peripheral neuropathy and the strength of such association.

Physicians have to deal with the specific challenge of effectively screening for diabetic neuropathy at an early stage, generally with 2–3 min tests, to stratify patients with symptoms, decide about specialty referral and treat the distressing symptoms accordingly. Several clinical and diagnostic techniques are used to confirm the presence of diabetic neuropathy and gauge its severity. Of these, a notable technique is the Michigan Neuropathy Screening Instrument (MNSI) which is a simple, cost-effective and validated bedside tool for detection of diabetic neuropathy. One study found it to have a sensitivity, specificity, accuracy and kappa value (over vibration perception threshold (VPT) and 10 g monofilament examination) of 78.15, 88.43, 83.33 and 0.67%, respectively [13]. The study employs this tool to gauge the presence and severity of diabetic polyneuropathy.

Aims and objectives

1. To study the prevalence of diabetic neuropathy in type 2 diabetics and describe its severity and frequency of different manifestations.
2. To study the correlation between severity of diabetic neuropathy and patient-related (age, gender, history of smoking, co-morbid illnesses, BMI, waist-to-hip ratio, lifestyle habits, family history of diabetes) and disease-related variables (duration of diabetes, control of diabetes, random and fasting blood sugar readings) and determine whether one or more of these can be used as predictors of severity of this disabling diabetic complication.

Materials and methods

Over a study period of March–June, 2015, all diabetic patients presenting to the outpatient department of KRL General Hospital and Centre for diabetes and liver diseases, Islamabad, were chosen to enter this study using convenient sampling. A total of 800 such patients were then screened for the presence or absence of diabetic neuropathy. All patients were required to provide informed consent. The hospital ethical committee approved the study. All patients were asked simple affirmative/negative questions relating to the presence of diabetic neuropathy using standardized tools (MNSI Performa provided in Annexure 1), and an MNSI score of >2 was used to diagnose diabetic neuropathy. Patient-related variables were noted. A thorough physical examination was performed on the index visit according to MNSI protocol.

It was a cross-sectional study.

Data were analyzed using SPSS v16.0. Qualitative variables were reported using percentages and quantitative variables by using mean ± standard deviation. Pearson and Spearman correlation coefficients were used to determine the presence and strength of correlation between outcome measure and parametric and nonparametric variables, respectively, and multivariate linear regression applied to determine predictors of diabetic neuropathy and reported using ANOVA (Analysis of variance). A p value of <0.05 was considered to be statistically significant.

Results

Demographic data

Out of the 800 diabetic patients screened for neuropathy, 90 were found to have diabetic neuropathy (11.25%). The mean age of the patients with diabetic neuropathy was 54.47 ± 10.87 years (range 27–86 years). Forty-one (45.5%) patients were males and 49 (54.4%) females. 71% of the population did not smoke. Coexistent morbidities included hypertension in 47.8% of the patients, ischemic heart disease in 7.8%, history of prior cerebrovascular accidents in 2.3% and chronic kidney disease (diabetic or otherwise) in 2.3%. 78.6% of patients with diabetic neuropathy had a family history of diabetes mellitus. The mean duration

Table 1 Neuropathy symptomatology reported by the patients

Symptom	Percentage of patients reporting the symptom (%)
Numbness of legs/feet	63.6
Burning pains in legs or feet	51.2
Sensitivity to touch	23.2
Pricking in legs or feet	52.3
Muscle cramps in legs or feet	53.8
Bed covers hurt on touching	16.7
Able to tell hot water from cold	84.8
Legs hurt on walking	54.4
Able to sense feet on walking	67.5
Weakness all over, most of the time	61.5
Symptoms worse at night	50
Dry, cracking feet	32.5
History of open sore on foot	14.3
History of amputation	4.7
Have been previously told to have neuropathy	15.6

of diabetes was 11.12 ± 9.8 years in the population with diabetic peripheral neuropathy (minimum—less than a year, maximum—62 years). All of the included patients were type 2 diabetics. 42.5% had a sedentary lifestyle, and 57.5% led a relatively active life. 76.5% did a weekly self-monitoring of blood glucose (SMBG) and 23.5% kept no such records. 34% were on insulin therapy for blood sugar controls. Average height was noted to be 161.67 ± 17.42 cm (range 106–249 cm), and the average weight was 85 ± 8.9 kg (range 51–98 kg). The average BMI was 29.59 ± 4.26 (range 22–41). Average waist/hip ratio was 0.98. Among the group, the average fasting blood sugar was 172 ± 71 mg/dL (minimum 72, maximum 415) and random measurements ranged between 95 and 537 mg/dL (average 256 ± 106). The average HbA1c value was 9.129 ± 2.4% (range 5.4–14%).

Symptomatology

63.6% patients had numbness in their legs and/or feet and 52.3% patients reported a pricking sensation in legs and feet. 23.3% patients had an enhanced sensitivity to touch in the affected body parts. 51.2% patients reported as having burning or electric current-like sensation in the peripheries. Muscle cramps were reported by 53.8% patients. 54.4% patients had legs that hurt on walking. 84.8% could perceive the difference between hot and cold using affected parts of the body.

61.5% patients said that they had generalized body weakness for most part of the day, and a total of 50% patients had worsening of the above-noted symptoms at night. 32.5% patients had dry, cracked feet. 14.3% reported a prior history of open wound/ulcer over their feet. 4.7% had had an amputation. Only 13.3% of the patients had previously been informed by their physicians about them having diabetic neuropathy as a complication of their disease (Table 1). The average MNSI score was 4.72 (range 2–10). 21.4% had been educated about foot care by their physicians. 11.8% had had prior access to health care. 7.1% reported social isolation due to a variety of medical and non-medical conditions. 28.6% reported bare foot walking; 37.2% had unsteady gait.

Physical examination

Of the sample population, 66.7% had had a single previous complete physical assessment and 33.3% had had two. 84% patients had normal feet on physical examination, 14.7% had deformities on either of the two feet and 38.7% had dry skin/callus. 10.7% had an infected wound on either of the two feet and 6.8% had ulcerations.

Ankle jerks were positive in 78.7% of the patients without reinforcement, present with reinforcement in 16% of the patients and absent in 5.3%. 6.8% of patients had an absent sense of vibration, 20.3% had reduced and 72% had a normal sense of vibration. Fine touch (monofilament) was intact in 63.2% of the patients reduced in 23.7% and absent in 13.2%. Average MNSI score on physical examination was 4.5 (range 0.5–9). 8.8% of these patients had asymmetrical findings. 5.1% had loss of mobility in either of the two feet.

7.2% of the patients had a severely reduced quadriceps femoris strength (MRC 0–2), 66.7% had moderately reduced (MRC 3) and 26.1% had a mildly reduced strength. 1.4% had severely reduced tibialis anterior strength, 68.6% had moderately reduced strength and 30% had mildly reduced strength.

Peripheral vascular disease

Right-sided dorsalis pedis pulse was impalpable in 1.2% of the patients, reduced in intensity in 13.6% and normal in 85.2%. Left dorsalis pedis was impalpable in 1.2%, reduced in 15.9% and normal in 82.9%. 1.2% had an absent right posterior tibial pulse, 12.5% had a weak and 86.2% had a normal right posterior tibial pulse. Similarly, 1.2% had an absent left posterior tibial pulse, 11.2% had weak and 87.5% had a normal left posterior tibial pulse.

Correlation between severity of neuropathy and disease/patient variables

Using multivariate regression, severity of diabetic neuropathy was found to have no correlation with gender, history of smoking, co-morbid illnesses, BMI, waist/hip ratio and random and fasting blood sugar readings as illustrated in Table 2.

Table 2 Variables with a lack of statistically significant correlation with severity of DPN

Variables	Pearson correlation coefficient	*p* Value
Gender	0.141	0.302
Hypertension	−0.461	0.360
IHD	−0.096	0.362
CKD	−0.523	0.109
Family history of diabetes	0.014	0.479
SMBG	−0.001	0.498
BMI	0.095	0.364
BSF	−0.224	0.202
BSR	−0.114	0.337

However, a significant positive correlation was found between duration of diabetes and severity of diabetic neuropathy ($r(75) = +0.699$, $p = 0.01$). This finding is shown in the graph below (Fig. 1). Using a linear regression analysis, duration of diabetes was found to be significant predictor of severity of diabetic neuropathy (total MNSI score) ($F(1, 71)$ 13.385 $p = 0.003$, $r^2 = 0.231$, adjusted $r^2 = 0.489$) and could account for 45.2% of total variance in the individual MNSI score by ANOVA.

Other variables correlating well with DPN severity were glycemic controls as expressed in terms of HbA1c (Fig. 2) and age (Fig. 3). For HbA1c, $F(2,13)$ 11.145, p value 0.002, adjusted $r^2 = 0.575$, and for age $F(3, 12)13.835$, p value 0.000, adjusted $r^2 = 0.720$, denoting that duration of diabetes, glycemic controls and age can together account for 72% of total variance in MNSI scores (Table 3).

We also found a statistically significant correlation between DNS scores and severity of diabetic neuropathy and noted that MNSI score on history was a significant predictor of MNSI score on physical examination and could account for 37.1% of the total variance in physical MNSI score ($p = 0.00$).

Lifestyle habits were found to correlate with symptomatology of diabetic neuropathy (MNSI score on history) but not with physical examination findings (MNSI score on physical).

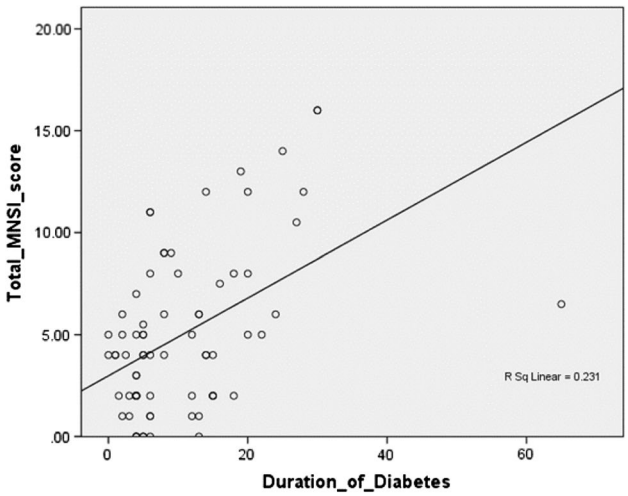

Fig. 1 Statistically significant correlation between duration of diabetes and severity of diabetic neuropathy (total MNSI score)

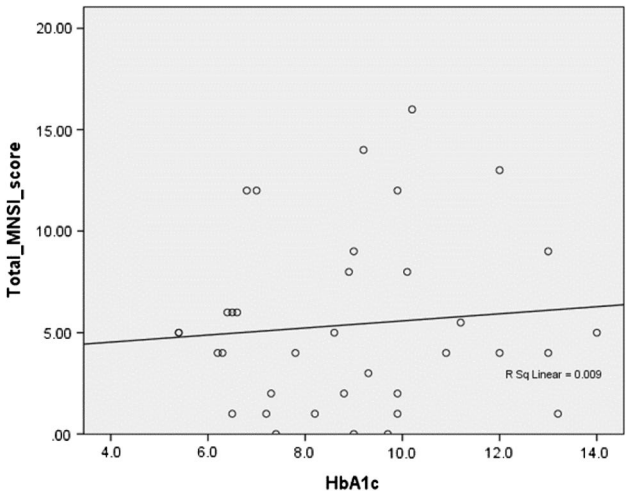

Fig. 2 Statistically significant correlation between severity of diabetic neuropathy (total MNSI score) and HbA1c levels

Discussion

Sensorimotor diabetic peripheral neuropathy is a frequently encountered complication of diabetes. In clinical practice, DSMN (diabetic sensorimotor neuropathy) has historically been diagnosed using symptoms, signs and electrophysiological testing. Quantitative sensory testing and consideration of intra-epidermal nerve fiber density and corneal confocal microscopy [14] are some of the other useful diagnostic tests [15]. The requirement of specially trained and experienced personnel or the use of invasive testing (for nerve or skin biopsies) makes such testing inconvenient, and extensive use in population-based real-world practice has fallen out of favor. The MNSI is one such reliable and simple screening tool which bypasses these difficulties on patients' and physicians' part.

Diabetic neuropathy and its complications cause significant morbidity. Symptoms are distressing, refractory to treatment and loss of protective sensation which result in increasing risk for foot ulceration and lower limb amputation. Subclinical neuropathy at an asymptomatic stage can explain the lack of beneficial effect of more intensive treatment/type of treatment.

The study was conducted at diabetic clinic, KRL General Hospital, Islamabad, and CDLD (Centre for diabetes

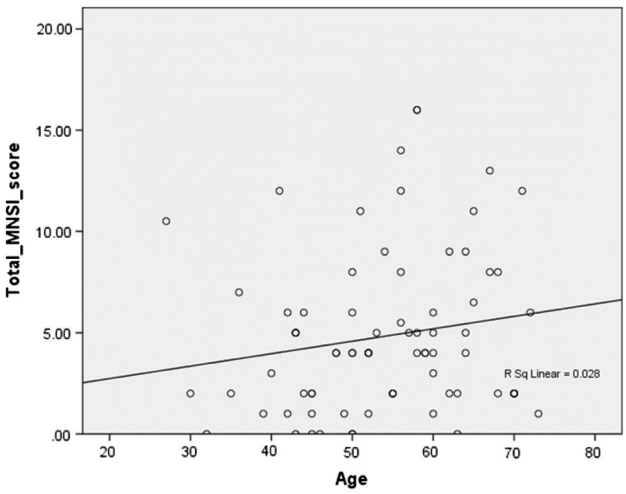

Fig. 3 Statistically significant correlation between severity of diabetic neuropathy (total MNSI score) and age

Table 3 Variables with a statistically significant correlation with severity of DPN

Variable	Pearson correlation coefficient	*p* value
Duration of diabetes	0.699	0.001
HbA1c	0.381	0.043
Age	0.525	0.018
Lifestyle	0.629	0.005

and Liver Diseases) which caters to patients of all socioeconomic strata, from Rawalpindi, Islamabad and its peripheries, to delineate the presence of neuropathy in patients with diabetes and describe its severity and correlates.

A total of 800 patients with diabetes were screened for neuropathy using a standardized tool—MNSI [16], and two trained clinicians. The prevalence of neuropathy in the cohort was found to be 11.25%. This is consistent with the previously published figures of 8% at the time of diagnosis increasing to 66% in those with increased disease duration [6, 7] although the cohort contained patients with both recent and relatively older diabetes diagnosis. Previously, prevalence as high as 59% has been reported [17].

The presenting symptoms in order of decreasing frequency were found to be numbness in legs/feet (63.6%), generalized body weakness (61.5%), pain, burning or electric current-like sensation in peripheries (51.2%) followed by muscle cramps which were found in 50.8%. This contrasts with the findings of a locally published study [18] which showed generalized pain as the most common symptom (8%) followed by numbness in 3%. 13.3% patients had previously been informed by their physicians as having diabetic neuropathy, and 11.8% had had prior access to health care. These observations show a stark contrast to those reported by George et al. [19] who found good knowledge score for diabetic neuropathy and foot care in 75% of patients reflecting a major need on the part of diabetologists and primary care physicians to make efforts to increase patient awareness about this illness. The MNSI score for symptomatology averaged at 4.72 (range 2–10). Comparison of this finding to previously known facts was not possible as the authors could not find any similar study in this regard.

On detailed physical assessment, the most common findings were dry skin/callus (38.7%) followed by deformities on either of the two feet (14.7%) and infected wound/ulcer in 10.7%. Loss of vibration perception which is considered the earliest manifestation of DPN was found in 6.8%, and vibration perception was reduced in 20.3% of the patients. Monofilament/fine touch was absent in 13.2% and reduced in 23.7%. Average MNSI on physical examination was 4.5. 7.2% had severely reduced quadriceps femoris strength, while 66.7% had moderately reduced muscle strength. 1.4% had severely reduced tibialis anterior strength, and 68.6% had moderately reduced muscle strength. Dorsalis pedis pulse was absent/weak in 14.8% of the patients, while 13.7% had a weak/absent posterior tibial pulse. There appears to be scarcity of literature studying the frequency of occurrence of these physical findings. The asymmetric nature of findings in 8.8% of the patients is comparable with 13% noted in a similar study [20].

As described earlier, impairment in glucostatic pathways and subsequent chronic hyperglycemia contributes significantly to the axonal damage that underlies the development of diabetic polyneuropathy. It is, therefore, sensible to imply a correlation between average or single blood glucose readings and the severity of diabetic polyneuropathy. Our study, however, fails to simulate the pattern shown in a previously published study which states glycemic control as a better predictor of severity of diabetic polyneuropathy than the duration of diabetes [21] by demonstrating a stronger correlation between the severity of diabetic neuropathy and duration of diabetes than with the glycemic controls. But, one study [22] has reported a failure of near normoglycemia in preventing the development of diabetic complications, hence indirectly supporting our observation. Also such an association between diabetic controls and development of diabetic neuropathy is said to be weaker in type 2 diabetics (the population included in this study) as compared to type 1 diabetics hence supporting our findings [23]. Discordance in impact of prior treatment may reflect deficiencies in susceptibility of small or large nerve fibers to glycemic exposure. In general, findings from studies of diabetic neuropathies have to be interpreted with caution given the broad range of diagnostic methods employed and lack of consistency in the criteria used to define neuropathy.

DCCT/EURODIAB [24] also reported that HbA1c was an important determinant of neuropathy incidence. DCCT/EURODIAB confirms that glycemic control is a significant

and robust predictor of neuropathy. Current strategies for optimizing glucose control are insufficient to fully prevent or delay the development of neuropathic complications.

Conclusion

Duration of diabetes, rather than the level of control of diabetes may be a better predictor of development and severity of diabetic peripheral neuropathy. This fact undermines the importance of achieving near normoglycemia and emphasizes the need of primary prevention and risk factor control to delay the development of diabetes in order for our population (which is facing an increased risk for developing this disease) to avert this debilitating diabetic complication.

Authors' contributions All the authors contributed equally to this work; they designed the article, did data collection, did thorough search, analyzed the data, wrote, reviewed and approved the final form of this manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Watson JC, Dyck PJB (2015) Peripheral neuropathy: a practical approach to diagnosis and symptom management. Mayo Clinic Proc 90(7):940–951
2. Martyn CN, Hughes RA (1997) Epidemiology of peripheral neuropathy. J Neurol Neurosurg Psychiatry 62:310–318
3. Italian General Practitioner Study Group (IGPSG) (1995) Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions, I: prevalence and general characteristics of the sample. Neurology 45:1832–1836
4. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383–393
5. Tesfaye S, Boulton AJ, Dyck PJ et al (2010) Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 33:2285–2293
6. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M (1995) Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 333:89–94
7. Boulton AJM (2005) Management of diabetic peripheral neuropathy. Clin Diabetes. 23:9–15
8. Boulton AJ, Vinik AI, Arezzo JC et al (2005) Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 28:956–962
9. Davies JL, Clark VM et al (2006) Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. Diabetes Care 29:2282–2288
10. Gaballa MR, Farag YM (2013) Predictors of diabetic nephropathy. Cent Eur J Med 8(3):287–296
11. Viberti GC, Jarrett RJ, Mahmud U, Hill RD, Argyropoulos A, Keen H (1982) Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. The Lancet 319(8287):1430–1432
12. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH (2005) Vascular risk factors and diabetic neuropathy. N Engl J Med 352(4):341–350
13. Jia WP et al (2006) Evaluation of the four simple methods in the diagnosis of diabetic peripheral neuropathy. Zhonghuayixuezazhi 86(38):2707–2710
14. Ahmed A, Bril V, Orszag A et al (2012) Detection of diabetic sensorimotor polyneuropathy by corneal confocal microscopy in type 1 diabetes: a concurrent validity study. Diabetes Care 35:821–828
15. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P (2010) Toronto diabetic neuropathy expert group. Diabetes Care 33(10):2285–2293
16. Lee CC, Perkins BA, Kayaniyil S, Harris SB, Retnakaran R, Gerstein HC et al (2015) Peripheral neuropathy and nerve dysfunction in individuals at high risk for type 2 diabetes: the PROMISE cohort. Diabetes Care 38(5):793–799
17. Dyck PJ, Kratz KM, Karnes JL et al (1993) The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology 43:817–824
18. Ishaq M, Khan GJ, Rahman S, Zulfiqar S (2013) Prevalence of complications in type 2 diabetes mellitus patients. Pak J Physiol 9(2):35–37
19. George H, Rakesh P, Krishna M et al (2013) Foot Care knowledge and practices and the prevalence of peripheral neuropathy among people with diabetes attending a secondary care rural hospital in Southern India. J Fam Med Prim Care 2(1):27–32. doi:10.4103/2249-4863.109938
20. Tracy JA, Dyck PJB (2008) The spectrum of diabetic neuropathies. Phys Med Rehabil Clin Am. doi:10.1016/j.pmr.2007.10.010
21. Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ (1999) Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. Diabetes Care 22(9):1479–1486
22. Ziegler D, Behler M, Schroers-Teuber M, Roden M (2015) Near-normoglycaemia and development of neuropathy: a 24-year prospective study from diagnosis of type 1 diabetes. BMJ Open. 5(6):e006559. doi:10.1136/bmjopen-2014-006559
23. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M (1995) Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 333(2):89–94
24. Martin CL, Albers JW, Pop-Bussi R (2013) Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 37:131–138