Prevalence of Peripheral Neuropathy in Diabetic Patients

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Abstract

Objective: Diabetic peripheral neuropathy is the main risk factor of diabetic foot ulcer and its early diagnosis is important to prevent limb amputation. We assessed the prevalence of peripheral neuropathy in diabetic patients.

Materials and methods: This cross-sectional study was performed on 352 randomly selected diabetic patients using a standardized questionnaire including age, gender, duration of diabetes, BMI, smoking status, HbA1c, fasting blood glucose, serum creatinine, triglyceride, cholesterol and uric acid as well as past medical history. Peripheral neuropathy was evaluated using United Kingdom Neuropathy Score screening test and 10 gram Semmes Weinstein monofilament tests. Ankle-Brachial Index was also used for detecting peripheral arterial disease.

Results: Forty-eight percent of patients were male and 52% were female; Mean age of the subjects was 57.0±10.3 with a median duration of diabetes of 12.6±7.5 years. The overall prevalence of neuropathy was 59.3%; 40.3% of patients failed to sense the monofilament. There was a statistically significant correlation between the results of United Kingdom Neuropathy Score screening test and 10-point monofilament testing (r=0.43, P<0.001). The prevalence increased with age, from 5.6% in the participants aged less than 40 years to 51.8% in patients more than 60 years. Neuropathy was associated with duration of diabetes, and was present in 14.1% and 34% of patients with diabetes duration less than 5 years and greater than 15 years, respectively. The prevalence of neuropathy was not significantly different between men and women.

Conclusion: Our study showed significant correlation between neuropathy and history of cerebrovascular accident. Diabetic peripheral neuropathy is a common complication associated with diabetes. It increases with both age and duration of diabetes.

Keywords: Diabetes, Peripheral neuropathy, Duration of diabetes, Prevalence

Introduction

Peripheral neuropathy is one of the most common complications of diabetes (1). It is characterized by a progressive loss of distal sensation that leads to formation of muscle and joint disorders, foot ulcer and amputation (2,3). Some patients have few complaints, but the physical examination reveals mild to moderately severe sensory loss. When symptoms are present, they may be negative or positive. Negative symptoms

include loss of sensation and strength, while positive symptoms include pain or pricking (4). Chronic painful neuropathy can cause symptoms for a long time and severely impair quality of life (5).

The prevalence and pattern of peripheral neuropathy varies widely in different studies (6-10). This diversity is due to the small size of studies, different diagnostic criteria and methods of selection of patients. Some authors have considered painful symptoms as diagnostic criteria; others have required sign of nerve dysfunction (11). The prevalence of neuropathy varies from as low as 1.55% to as high as 100% in patients with type 2 diabetes (6,12-14) depending on the difference in screening approaches, diagnostic criteria and study population (14). Up to 7.5% of diabetic patients have clinical neuropathy at the time of diagnosis. This rate increases to 50% among patients who had diabetes for 25 years (6). Because of the potentially severe complications of peripheral neuropathy, including limb amputation due to infected non-healing ulcers, early diagnosis of peripheral neuropathy is important. According to American Diabetic Association, all patients with diabetes should be screened for neuropathy at diagnosis of type 2 diabetes and five years after diagnosis of type 1 diabetes (15). There are different screening tests for diabetic peripheral neuropathy (DPN), but most of them are not practical in routine clinical practice. The need to identify simplified criteria has resulted in development of two simple screening tests; one was developed at Michigan (16) and another in the United Kingdom (17). Due to different methods for diagnosis of peripheral neuropathy, the prevalence of peripheral neuropathy in Iran has been differently reported. This study assessed the prevalence of DPN based on United Kingdom Neuropathy (UKN) Scores and monofilament test as well as the related factors.

Materials and Methods

In this cross-sectional study, 352 diabetic patients referred to our center were recruited consecutively from November 2007 to July 2010. Patients consented to and completed a questionnaire including demographic information, medication and history of medical disorders.

The sample size was estimated based on proportion of DPN among type 2 diabetic patients detected by monofilament or UKN score in previous studies in Iran (29-30) using 0.05 precision and power of 0.80. Excluded were patients with history of hereditary or acquired neuropathy, vasculitis, amyloidosis and hypothyroidism. Informed consent was obtained from all subjects and the research had the approval from the institutional review board and ethics committee of the respective university and was carried out in accordance with the Declaration of Helsinki.

The ankle-brachial index (ABI) for each leg was calculated by the higher systolic blood pressure (SBP) in the dorsal or posterior tibial arteries, divided by the higher value of the two arm SBPs. The higher arm SBP was used because of the variation in arm blood pressures and the strong association between peripheral arterial disease (PAD) and subclavian stenosis (18). If ABI was 0.9-1.3 we interpreted as normal group and when ABI was < 0.9 in each leg or ABI >1.3 and toe-brachial index (TBI) less than 0.6 we considered as subjects with PAD (19).

Doppler ultrasound (Multi/Super Duplex II) was used to measure the systolic blood pressure on bilateral brachial, posterior tibial and dorsal pedis in a supine position after a 5-minutes rest. Peripheral Neuropathy was assessed by UKN score and monofilament test.

United Kingdom Neuropathy Score Screening Test

Neuropathy disability score and neuropathy symptom score for each patient was derived as the following.

Neuropathy disability score (NDS)

This score was obtained through examination of the ankle reflex, vibration, pinprick and temperature (cold tuning fork) sensation at the

great toe. Sensory quality were scored as either present=0, reduced/absent=1 for each foot, and reflexes as normal=0, present with reinforcement=1 or absent=2 per side. So the total maximum abnormal score was 10. A score of 3-5 was regarded as evidence of mild neuropathy sign, 6-8 as moderate and a score of 9-10 as severe sign of neuropathy.

Neuropathy symptom score (NSS)

Patients were asked about their experience of pain or discomfort in the legs: if the patients explain burning, numbness or tingling as score of 2 was assigned; fatigue, cramping or aching scored 1. The existence of symptoms in the feet was taken a score of 2, the calves 1, and elsewhere a score of 0. Nocturnal exacerbation of symptoms scored 2 versus 1 for both day and night and 0 for day alone. A score of 1 was added if the symptoms had ever woken the patient from sleep. The patients were asked if any maneuver could decrease the symptoms: walking was assigned a score of 2; standing was 1 and sitting or lying down as 0. The maximum symptom score was 9.

A symptom score of 3-4 was taken to imply mild symptoms, 5-6 moderate symptoms, and 7-9 severe symptoms.

Diagnosis of peripheral neuropathy

The minimum acceptable criteria for a diagnosis of peripheral neuropathy were moderate sign with or without symptoms, or mild signs with moderate symptoms (20).

Assessment of neuropathy by monofilament test

Neuropathy was defined as the loss of protective sensation determined by application of 10-gram Semmes Weinstein monofilament wire system on ten sites of each foot. Patients who were unable to sense the monofilament on three or more sites were defined as insensate (21). All above-mentioned tests were performed by the same investigator to control for inter-rate reliability.

Risk factors of peripheral neuropathy were assessed using the following data: gender, age, duration of diabetes, BMI and smoking status. After obtaining an informed consent, fasting blood sample was taken for measuring of fasting blood glucose, hemoglobin A1c, serum creatinine, triglyceride, cholesterol and uric acid. The history of ischemic heart disease and cerebrovascular disease was defined as having a past history of myocardial infarction, angina pectoris, coronary bypass grafting, and cerebrovascular accident (11).

Statistical analysis

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS version 12.0, Chicago, IL). Chi-square test was used to compare discrete variables. One-way ANOVA analysis and Kruskal-Wallis tests were used to compare different risk factors in diabetic patients stratified by ABI. We used multiple regression analysis to evaluate independent risk factors of PAD. $P<0.05$ was considered significant. Data are presented as mean±SD. Pearson correlation test was used to assess correlation between UKN score and monofilament test.

Results

The mean age of diabetic patients and mean diabetes duration were 57.0±10.3 and 12.6±7.5 years, respectively. Fifty-two percent of the subjects were women and 48% men. The prevalence of peripheral neuropathy according to the UKN score was 59.3% (95%CI: 50.4-67.3). 40.3% (95%CI: 35.3-45.3) of patients failed to sense 10-gram Semmes Weinstein monofilament. Pearson correlation tests revealed a statistically significant correlation between the results of UKN score and 10-point monofilament testing (r=0.43, $P<0.001$).

The prevalence of neuropathy increased with age from 5.6% in those patients aged less than 40 years, to 51.8% in aged more than 60 years. DPN was also more prevalent with increasing duration of diabetes, from 14.1% in patients with diabetic duration less than 5 years to 34% in patients with diabetes more than 15 years. There was no significant difference between males and females.

Table 1 shows Clinical and biochemical characteristic of the neuropathy and non neuropathy groups of type 2 diabetic patients. The age and duration of diabetes in patients with DPN were higher than subjects without neuropathy.

Table 2 shows the odds ratio of risk factors in patients with peripheral neuropathy. This study demonstrated the patients more than 50 years had 2.94 folds peripheral neuropathy compared to subjects less than 50 years. The prevalence of neuropathy in patients with duration of diabetes more than 15 years was 2.5 folds of patients with duration of diabetes less than 5 years. Positive history of cerebrovascular accident in patients with neuropathy was 3 folds of patients without neuropathy.

Multiple logistic regression analysis of risk factors of neuropathy, using sex, age, duration of diabetes, history of ischemic heart disease and cerebrovascular accidents showed age and duration of diabetes were the main risk factors associated with peripheral neuropathy. Odds ratios of age more than 50 years and duration of diabetes more than 15 years were 3 and 2.43, respectively (table 3).

In our study, 27.6% of diabetic patients had

Table 1. Clinical and biochemical characteristic of type 2 diabetic patients with and without neuropathy.

Risk Factors	Neuropathy		*p*-value
	Present	Absent	
Sex (Male/Female) (%)	49/51	46/54	0.58
Age (year)	58.9±9.7	52.6±9.3	0.001*
Diabetes Duration (year)	13.6±7.2	10.7±7.4	0.001*
BMI (kg/m^2)	26.6±3.4	28.4±5.2	0.1
Smoking ever/never (%)	12.1/87.9	9.6/90.4	0.47
CHD History (%)	17.9	18.2	0.912
Stroke History (%)	14.3	5.8	0.221
ABI	1.1±0.14	1.1±0.17	0.21
HbA1c (%)	7.6±1.9	7.9±1.8	0.46
FBS (mg/dl)	177±61.4	177±60.7	0.99
2hPP (mg/dl)	262.4±84.8	260.1±81.8	0.84
TG (mg/dl)	192.1±88.7	220.4±151.9	0.06
TC (mg/dl)	183.9±42.4	188.9±49.5	0.39
HDL (mg/dl)	48.9±15.1	54.3±18	0.03*
LDL (mg/dl)	94.9±33.1	93.7±40.5	0.83
Creatinine (mg/dl)	0.97±0.32	0.98±0.26	0.87
BUN(mg/dl)	21.7±9.8	18.3±7.4	0.16

*P<0.05; Data are presented as Mean±SD.

BMI: Body Mass Index; CHD: Coronary Heart Disease; ABI: Ankle-Brachial Index; FBS: Fasting Blood Sugar; TG: Triglyceride; TC: Total Cholesterol; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; BUN: Blood Urea Nitrogen.

Table 2. Odds ratios and their 95% CI risk factors for neuropathy groups in patients with type 2 diabetes.

Risk Factors	Change of Risk Factors	Neuropathy	
		OR (95%CI)	*p*-value
Age	<50*	---	---
	≥50	2.94(1.7-5)	0.001
Sex	male vs. female	1.1 (0.7-1.7)	0.58
Diabetes Duration (year)	<5 *	---	---
	5-15	1.53 (0.83-2.9)	0.18
	>15 years	2.5(1.2-5)	0.01
BMI (kg/m^2)	<25 *	---	---
	25-29 kg/m^2	5.8(0.68-52.6)	0.08
	≥30 kg/m^2	3.57 (0.32-50)	0.29
CHD History	Yes vs. No	1.4 (0.8-2.5)	0.2
Stroke History	Yes vs. No	3 (1-9.2)	0.04
History of Smoking	Yes vs. No	1.29 (0.63-2.6)	0.47

*Reference Category

CHD: Coronary Heart Disease

foot deformity. This study showed that age more than 50 years, duration of diabetes more than 5 years and neuropathy were the main risk factors for foot deformity. This study also demonstrated that 23% of patients had foot ulcer. 90.3% of patients with foot ulcer were more than 50 years, 6.7% had duration of diabetes less than 5 years, and 60% had duration of diabetes of 5-15 years and 33.5% more than 15 years.

The principal factors for foot ulcer in our study were age >50 years, neuropathy and peripheral vascular disease.

Discussion

Diabetes is a common cause of peripheral neuropathy. The prevalence of peripheral neuropathy is reported between 8 and 50% (21,22) but that of neuropathy is as high as 84.8% (23). In a landmark study, over 440 patients with diabetes were serially evaluated over 25 years; neuropathy was defined as decreased sensation in the feet and depressed or absent ankle reflexes showed the onset of neuropathy, and was positively correlated with the duration of diabetes and by 25 years 50% of patients had neuropathy (24-26). In EURODIAB IDDM complication study, the prevalence of peripheral neuropathy was 28% and significant correlation were observed between neuropathy and age, duration of diabetes, and quality of metabolic control (27). There are conflicting reports regarding the frequency of peripheral neuropathy with age, gender, hypertension and hyperlipidemia (21,22). Generally, the frequency is higher in patients over 70 years. The Pittsburg Epidemiology of Diabetes Complication Study of 400 patients with diabetes reported that the prevalence of neuropathy was 34% (8). Two reports evaluated the incidence of new case of diabetic neuropathy. In one, in which 231 patients with type 2 diabetes were followed for a mean of 4.7 years, the incidence of DPN was 6.1 per 100 person-year (28).

The present study reported the prevalence rate of peripheral neuropathy in our patients to be about 59.3% based on UK scoring systems and 40.3% of patients failed to sense 10-gram Semmes Weinstein monofilament. Our results are in agreement with Tabatabaei et al. study that demonstrated the prevalence of DPN based on UKN score system and monofilament test was 54% and 31.7% respectively (29). Kiani et al. demonstrated the prevalence of DPN in type 2 diabetic patients according to standard NSS and Neuropathy Disability Score (NDS) criteria was 49.3% (30). Janghorbani et al. showed the prevalence of DPN was 75.1% (31). Majumder et al. showed the prevalence of severe peripheral neuropathy among diabetic patients for over 15 years on the basis of loss of vibration sensation was 19% and only 6% had no neuropathy (32).

These differences may be due to that each method has a unique way of detecting neuropathy; in the symptom score, the result depends on what patients say and in the sign score, the examiner plays the major role. Another reason, some methods such as deep tendon reflexes, is examiner-dependent and

Table 3. Multivariate Logistic regression analysis of Independent risk factors for neuropathy in patients with diabetes.

Risk Factors	Change of Risk Factors	Neuropathy	
		OR (95% CI)	*P*-value
Age (year)	<50*	---	---
	≥50	3(1.7-5.1)	0.001
Sex	male vs. female	1.17 (0.7-1.9)	0.53
Diabetes duration (year)	<5 *	---	---
	5-15	1.53 (0.81-2.8)	0.18
	>15 years	2.43(1.2-4.9)	0.01
CHD History	Yes vs. No	0.85 (0.46-1.55)	0.6
Stroke History	Yes vs. No	2.7 (.9-8.3)	0.08
History of smoking	Yes vs. No	1.66 (0.7-5)	0.23

*Reference Category
CHD: Coronary Heart Disease

may include inter-personal bias.

In our study, the prevalence of DPN was 59.3% and there was a significant relationship between neuropathy and age; but there was no significant relationship between neuropathy and gender. This study showed a significant correlation between neuropathy and duration of diabetes. Some studies demonstrated smoking was associated with neuropathy but in our study no significant association was found. The results of our study showed the main risk factors for diabetic foot deformity was neuropathy, duration of diabetes and age. There was not significant association between HbA1c, triglyceride, cholesterol, uric acid, creatinine and neuropathy. We could not find significant correlation between foot deformity and ulceration. Our study has some limitations. We did not use nerve conduction velocity (NCV) for diagnosis of peripheral neuropathy and it was a cross-sectional study; so, we need a cohort research to assess the effect of risk factors on the incidence of peripheral neuropathy.

In conclusion, DPN is a common complication associated with diabetes. It increases with both age and duration of diabetes. The main risk factors for diabetic foot ulcer in our study were PAD, neuropathy and duration of diabetes.

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References

1. Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, et al.The North-West Diabetes Foot Care Study: incidence of, and risk factors for new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002;19(5):377-84.
2. Poncelet AN: Diabetic polyneuropathy: risk factors, patterns of presentation, diagnosis and treatment (Review). Geriatric. 2003;58:16-8
3. Vilekyte L, Rubin RR, Leventhal H: Psychological aspects of diabetic neuropathic foot complications: an overview. Diabetes Metab Res Rev. 2004;20(1):13-8.
4. Melton LJ III, Dyck PJ. Epidemiology. In: Dyck PJ ,Thomas PK, Asbury AK, Winegrad AI, Porte DJr. Diabetic neuropathy. Philadelphia, PA: Saunders; 1987;27-35.
5. Benbow SJ, Wallymahmed ME, Macfarlane IA. Diabetic peripheral neuropathy and quality of life. J Med. 1998;91:733-7.
6. Pirat J. Diabetes and its degenerative complication: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978;1:168-88.
7. Franklin GM, Kahn LB, Bacter J, Marshall JA, Hamman RF. sensory neuropathy in non insulin dependent diabetes mellitus. The San luis Valley study. Amer J Epidemiol. 1990;131:633-43.
8. Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes. 1989;38(11):1456.
9. Boulton AJ, Vinik AI, Arezzo JC. Diabetic neuropathies; a statement by the American Diabetes Association. Diabetes Care.2005;28:956.
10. Lehtinen JM, Uusitupa M, Siitonen O, Pyörälä K. Prevalence of neuropathy in newly diagnosed NIDDM and nondiabetic subjects. Diabetes 1989;38:1307-13.
11. Edmonds ME, Bludell MP, Morris ME, Thomas EM, Corton LT, Watkins PJ. Improved survival of the diabetic foot: the role of a specialized foot clinic. Q J Med. 1986;60:763-71.
12. Harris MI, Estman R, Cowie C. Symptom of sensory neuropathy adults with NIDDM in the U.S. population. Diabetes care. 1993; 16(11):1446-52.
13. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various type of diabetic neuropathy in a population based cohort: The Rochester Diabetic neuropathy study Neurology.1993;43:817-24.
14. Thomas PK, Eliasson SG. Diabetic neuropathy. In: Dyck PJ, Thomas PK, Asbury A, Weingard A, Porte D Jr, eds. Diabetic neuropathy. Philadelphia,PA:Saunders;1987. 1773-810.
15. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005; 28:956.
16. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care. 1994;17(11):1281-9.

17. Young M j, Boulton A J,Macleod A F, Williams D R, Sonksen P H. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36:150-4.
18. Shadman R, Criqui MH, Bundens WP, Fronek A, Denenberg JO, Gamst AC, et al. Subclavian artery stenosis: prevalence, risk factors, and association with cardiovascular diseases. Journal of the American College of Cardiology 2004;44(3):618-23.
19. American Diabetes Association. Peripheral Arterial Disease in People with Diabetes. Diabetes Care. December 2003; 26:3333-41.
20. Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening test for peripheral neuropathy in the diabetic clinic. Diabetes Care. 2001;24:250.
21. Chang C, Lu F, Yang YC, Wu Js, Wu TJ, Chen MS, et al. Epidemiologic study of type 2 diabetes in Taiwan. Diabetes Res Clin Pract. 2000;50(2):49-59.
22. Shaw JE, Hodge AM, de Courten M, Dowse GK, Gareeboo H, Tuomilehto J, et al. Diabetic neuropathy in Mauritius: Prevalence and risk factors. Diabetes Res Clin Pract. 1998;42:131-9.
23. Palumbo PJ, Elveback LR, Whisnat JP .Neurology complication of diabetes mellitus: transient ischemic attack, Stroke and peripheral neuropathy. Adv Neurol. 1978;19:593-601.
24. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (author's transl). Diabete Metab. 1977;3(2):97.
25. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (2nd part) (author's transl). Diabete Metab. 1977;3(3):173.
26. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl). Diabete Metab. 1977;3(4):245.
27. The EURODIAB IDDM Complications Study Group. Microvascular and acute complications in IDDM patients. Diabetologia. 1994;37:278.
28. Sands ML, Shetterly SM, Franklin GM, Hamman RF. Incidence of distal symmetric (sensory) neuropathy in NIDDM. The San Luis Valley Diabetes Study. Diabetes Care. 1997;20(3):322.
29. Tabatabaei-Malazy O, MR Mohajeri-Tehrani MR, Madani SP, Heshmat1 R, Larijani1B. The Prevalence of Diabetic Peripheral Neuropathy and Related Factors. Iranian J Publ Health, 40(3),2011,55-62
30. Kiani J, Moghimbeigi A, Azizkhani H, Kosarifard S. The Prevalence and Associated Risk Factors of Peripheral Diabetic Neuropathy in Hamedan, Iran Archives of Iranian Medicine (AIM); 2013,16(1);17
31. Janghorbani M, Rezvanian H, Kachooei A, Ghorbani A, Chitsaz A, Izadi F, Amini M. Peripheral neuropathy in type 2 diabetes mellitus in Isfahan, Iran: prevalence and risk factors. ActaNeurol Scand, 2006 Dec;114(6):384-91.
32. Majumder A, Chattejee S, Maji D. Peripheral neuropathy in diabetes. J Indian Med Assoc. 2013 Jun;111(6):382, 384-6.