Original Research

Risk factors of peripheral neuropathy in patients with type 2 diabetes in Isfahan: Results of a cohort study in Iran

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ABSTRACT

Introduction: Peripheral neuropathy (PN) is among the most prevalent complications of diabetes that can lead to impairment of mobility of diabetic patients. The purpose of the current study was to predict relative factors influencing the occurrence of peripheral neuropathy (PN) in patients with type 2 diabetes.**Methods:** This was a cohort study on diabetic patients in the Isfahan Province of Iran. The studied population consisted of patients with type 2 diabetes, of ages 18 or older, who were diagnosed as new cases of diabetes from 2007 to 2014, and whose follow-up was completed by the end of 2016. In this study, with regards to the presence of time-varying co-variates, time-dependent Cox regression model was employed in order to estimate the Hazard Ratio (HR) of PN in the diabetic patients. **Results:** Overall, 1874 patients with diabetes participated in the study, of which 839 (44.77%) were men and 1035 (55.23%) were women. During the study period, PN occurred in 17.98% of the patients; the ratio was 17% in women and 19.18% in men. In comparison to the reference group, the adjusted HR of PN in males was equal to 3.66 (95% CI: 1.15-11.67), in housewives was equal to 4.09 (95% CI: 1.02-16.38), and divorced or wife died patients was equal to 3.02 (95% CI: 1.61-5.65). In addition, for each 6 month follow-up of the patients, the adjusted HR of PN increased to 1.19 (95% CI: 1.17-1.22). **Conclusions:** The adjusted HR of PN in men, in housewives, and elderly people, divorced or wife died patients, with elementary education level were greater than the reference group. Thus, training, screening and diagnostic programs should be carried out with greater sensitivity in patients who are at greater risk for PN.

Key words: Cohort study, Peripheral neuropathy, Risk factors, Time dependent Cox regression model, Type 2 diabetes

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INTRODUCTION

Diabetes includes a group of metabolic disorders that is associated with high blood glucose levels and impaired carbohydrate, lipid and protein metabolism. It is a disease that results from a disorder in the function or secretion of insulin. The two common groups of diabetes are known as type 1 (diabetes dependent on insulin) and type 2 (diabetes not dependent on insulin) [1]. According to the existing estimates, in 2011 more than 366 million people all over the world had diabetes and this number will increase up to 522 million people by 2030 [2].

Peripheral neuropathy (PN) is among the most prevalent complications of diabetes that can lead to impaired mobility of patients with diabetes [2,3]. The prevalence of PN is different in numerous studies and also differs from country to country; the prevalence has been reported to be between 1.5 to 80% [4–8]. PN involves about 37% of patients with type 1 diabetes, and at least 20-40% of patients with type 2 diabetes [9]. The prevalence of PN was equivalent to 34% in the study carried out by Nitiyanant *et al.* that evaluated the control of diabetes across 230 diabetes care centers in 12 Asian countries [10]. In a review study, which used the meta-analysis method to assess the results of 21 studies conducted in Iran from 1991 to 2013, the prevalence of diabetic-associated PN was estimated to be about 53%. Therefore, based on the results of that study, it can be stated that the prevalence of PN in Iranian patients is high; as such, more than half of the patients with diabetes have PN [11].

In the European Diabetes (EURODIAB) Prospective Complications Study, in which 1172 patients were followed for 7 years, the cumulative incidence rate of PN was equivalent to 23.5% [12]. According to the results of that study, the risk of having PN was related to the level of glycated hemoglobin (HBA1c) and the duration of diabetes [13]. Moreover, in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, it was observed that the cumulative incidence of PN after 4-year follow-up of the diabetic patients was about 13% [13] and after 10 years of follow up, it increased up to 34.2% [14].

Therefore, in light of the high prevalence of type 2 diabetes and importance of PN in diabetic patients and that, thus far, limited studies have been conducted to determine the factors affecting the occurrence of PN in patients with diabetes in Iran, this current study was conducted with the aim of examining the incidence rate and factors of PN occurrence in patients with type 2 diabetes in Isfahan, Iran. The results of this

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study could help to identify the people most at risk for PN in order to accelerate initiation of effective diagnostic and therapeutic interventions. This should decrease the incidence of PN in diabetic patients, as well as improve the quality of life and survival of these patients.

METHODS

Research design and data source

This is a cohort study on diabetic patients living in the Isfahan province of Iran. After the diagnosis of diabetes, a file called "diabetic's file" was created for each diabetic in the Diabetic Patient Care Program in the healthcare system of Iran. In this study, data of the assessed variables were extracted by the researcher from the diabetic patient's records. For time-varying variables, collection of data was conducted through repeated measurements at a time interval of 6 months until the end of the follow-up period. Furthermore, the information about occurrence of PN was extracted from the patient's files and referral forms to specialists.

Study population

The study population consisted of patients with type 2 diabetes mellitus (ages 18 or older) who were diagnosed as new cases of diabetes from 2007-2014 and who were registered in diabetes files of health centers, health houses, and diabetes clinics. These patients received regular health care (at least once every 180 days) for a minimum of 2 years. Patient follow-up was done by the end of 2016.

Inclusion criteria of the study

1. Patients with type 2 diabetes mellitus, of ages 18 or older.
2. Newly diagnosed patients from 2007-2014 as a new case of diabetes.
3. Patients registered in diabetes files of health centers, health houses, and diabetes clinics, and who were referred regularly to receive health care services.
4. Patients residing in the Isfahan province (of Iran).

Exclusion criteria of study

1. Dialysis patients
2. Patients who did not regularly follow clinical and laboratory examinations for at least once every 6 months.

Censored patients in the research were as follows

1. Patients who missed the follow-up period.
2. Patients with no regular treatment.
3. Cases with no study outcomes until the end of the follow-up period.

Study variables

Time-varying variables or time-dependent variables included: Glycated hemoglobin (HbA1C), Fasting blood sugar (FBS), Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and type of diabetes treatment.

Basic variables of this study were as follows: Gender, residential place, occupation, educational level, marital status, smoking status, age, physical activity level (PAL), receiving aspirin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, cholesterol, lipid-lowering drugs, and basic values of time-varying variables.

The properties of the data collection tool and collection method: The data analyzed in the present study (demographics, clinical and para-clinical information of patients, *etc.*) were gathered by using a researcher-made checklist with the aid of the information from the files of families and/or the diabetes files of patients, or by phone calls with patients if the required information were not sufficient. Follow-up of patients continued until the end of study and/or occurrence of PN.

Peripheral neuropathy diagnosis

In the current study, the diagnosis of PN was carried out by a trained doctor, the Michigan questionnaire, and the monofilament test. Some information about the signs of PN in the diabetic patients, as well as the nail and skin conditions, were investigated via the Michigan questionnaire. In the Michigan questionnaire, 4 factors were addressed, namely the outer appearance of the foot skin (in terms of the skin's dryness or cracked skin, callus, infection, and/or deformity of body), existence of ulcer, reflex of Achilles Tendon, and situation of vibration feeling. The factors were assessed by utilizing 128 hertz diapason in the toe, and a score bigger than 2 was considered as PN existence [15]. In terms of PN, the ten-point monofilament test was performed in ten parts of the sole and back of the leg; the lack of monofilament at one or more points indicated PN [16].

Data analysis

In this study, use was made of the statistical chi-square test in order to assess the relations of qualitative variables. An independent t-test was employed to compare the means of quantitative variables in patients with PN versus patients without PN, as well among men and women. In this study, with regards

to the presence of time-varying co-variates, the time-dependent Cox regression method was employed in order to estimate the Hazard Ratio (HR) of PN in diabetic patients. The adjusted HR for any variable was adjusted for all other variables. The HR was calculated by considering the 95% confidence interval (CI). The significance level in all tests was considered as 5%. The statistical software SPSS 18 and Stata 15 were used for analysis of data.

RESULTS

Overall, 1874 patients with type 2 diabetes participated in the study. Of this total, 839 (44.77%) of the patients were men and 1035 (55.23%) were women. The average age of the study patients was 56.47± 15.69; it was 57.57 ± 15.19 in men and 55.57 ± 16.04 in women (p= 0.006; this difference was significant). The average age of the diabetic patients with PN symptoms was equivalent to 59.46 ± 15.13 years and in patients without PN was equivalent to 53.55±15.38 years; this difference was statistically significant (p=0.004). During the study period, PN occurred in 17.98% of the patients; from this proportion, 17% were women and 19.18% were men. The demographic, clinical and para-clinical properties of the study patients are observable in **Tables 1, 2 and 3**.

In comparing the average of quantitative variables between patients with PN and those without PN, it was observed that the patients with PN are older ($p \leq 0.001$) and have higher BMI (p=0.139), FBS ($p \leq 0.001$), HBA1c ($p \leq 0.001$), Cholesterol (p=0.065), LDL (p=0.068), SBP (p=0.001), and DBP (p=0.001), compared to patients without PN (**Tables 2 and 3**).

The incidence rates of PN in each 1000 person-year follow-up for the following groups were as follows: in men it was 37.91 (95% CI: 32.49-44.25), in women it was 34.61 (95% CI: 29.85-40.12), in urban patients it was 36.91 (95% CI:29.73-45.83), in rural patients it was 35.86 (95% CI:31.72-40.54), in diabetic patients with oral medicine regimen it was 34.38 (95% CI:30.44-38.83), in patients with oral medicines and insulin therapeutic regime, the incidence rate was 43.35 (95% CI:34.72-54.13), in patients with normal BMI it was 31.87 (95% CI:26.28-38.67), in overweight patients it was 38.24 (95% CI:32.60-44.85), in obese patients it was 38.56 (95% CI:31.10-47.83), in patients with low physical activity it was 37.47 (95% CI:33.13-42.37), in patients with moderate physical activity it was 32.12 (95% CI:24.99-41.28), in patients with high physical activity it was 32.58 (95% CI:18.91-56.10), and in patients with very high physical activity the incidence rate was equivalent to 35.29 (95% CI:18.36-67.83). The incidence rates based on all the studied variables are shown in **Table 4**.

In comparison to the reference group, the un-adjusted HR of PN in rural patients was equal to 0.96 (95% CI: 0.75-1.23), in men it was 1.09(95% CI: 0.88-1.35), in illiterate patients it was 3.02(95% CI: 1.71-5.32), in patients with elementary education it was 2.64(95% CI: 1.48-4.71), in patients with junior school education it was 2.11(95% CI:1.12-3.98), in patients with high school education it was 2.16(95% CI: 1.15-4.03), in retired patients it was 1.95(95% CI: 0.83-4.55), in housewives it was 1.83(95% CI: 0.86-3.90), in unemployed patients it was 2.42(95% CI: 1.11-5.29), in patients receiving blood anti-lipid drugs it was 1.28(95% CI: 1.03-1.64), in people receiving oral medicines and insulin for diabetes therapy it was 1.29(95% CI: 1.02-1.66), and in patients receiving aspirin it was equal 1.43(95% CI: 1.10-1.86). Moreover, the un-adjusted HR of PN for one-unit increase in BMI was equal to 1.019 (95% CI:0.995-1.044), for the FBS it was 1.02(95% CI: 1.01-1.03), for HBA1c it was 1.10(95% CI: 1.04-1.16), for LDL it was 1.002(95% CI: 0.999-1.005), for HDL it was 0.999(95% CI: 0.989-1.008), for SBP it was 1.014(95% CI: 1.006-1.023), and for DBP it was 1.016(95% CI: 1.007-1.026). The un-adjusted HR based on the other studied variables are observable in **Table 5.**

In comparison to the reference group, the adjusted HR of PN in males was equal 3.66 (95% CI:1.15-11.67), in housewives it was 4.09 (95% CI: 1.02-16.38), in unemployed patients it was 2.08 (95% CI: 0.93-4.67), in retired patients it was 1.65 (95% CI: 0.69-3.94), in self-employment patients was equal to 1.56 (95% CI: 0.71-3.43), in married patients was equal to 2.18 (95% CI: 1.24-3.83), and in divorced or wife died patients was equal to 3.02 (95% CI: 1.61-5.65). In addition, by increasing the follow-up of patients, the HR of PN increased such that in each 6-month follow-up, the adjusted HR of PN increased to 1.19 (95% CI:1.17-1.22) **Table 6.**

DISCUSSION

The current study examined the incidence rate and the factors influencing PN occurrence in patients with type 2 diabetes in Isfahan, Iran. During the study period, PN occurred in 17.98% of the patients. This proportion in women is 17% and in men is 19.18%. The incidence rates of PN in men, urban patients, people on oral medication and insulin therapeutic regimen, people who were overweight and/or obese, and people with low physical activity were higher than the other groups. In the multivariate time-dependent Cox regression model, it was observed that in comparison to the reference group, the HR of PN in men, housewives, divorced or wife died patients, and people with high school education level were much greater.

In a study conducted with Marvasti *et al.* in Isfahan, the cumulative incidence of PN during a 10-year follow-up was equivalent to 30.7%, and in other study (by Tesfaye *et al.*) the cumulative incidence of PN during a 7-year follow-up was equal to 23.5%[12]. In a study carried out by Lioyd *et al.* with 4 years of follow-up, the incidence of PN was 13%, and after a 10-year follow-up it was 34.2%[13]. Similarly, in a study by Sands et al., after 5-year follow-up of patients it was 28.6%[17].

Table 1: Demographic, clinical and paraclinical characteristics of the studied patients

Variables	Total
Residential place	
Rural	1417(75.62)
Urban	457(24.38)
Gender	
Male	839(44.77)
Female	1035(55.23)
Educational level	
Illiterate	751(40.07)
Elementary school (one to five years learning)	470(25.08)
Junior school (six to nine years learning)	197(10.51)
High school (ten to twelve years learning)	234(12.48)
Academic education	222(11.84)
Occupation	
Governmental	54(2.88)
Self-employment	458(24.43)
Housewife	931(49.70)
Unemployed	288(15.36)
Retired	143(7.63)
Marital status	
Married	1295(69.10)
Single	306(16.32)
Divorced or widow	273(14.56)
Smoking status	
smoker	182(9.71)
Non-smoker	1692(90.29)
Physical activity level	
Low	1379(73.58)
Moderate	369(19.69)
High	72(3.84)
Very high	54(2.88)
Lipid-lowering drugs	
No	1526(81.43)
Yes	348(18.56)
Type of diabetes treatment	
Oral medicines	1609(85.85)
Oral medicines and insulin	265(14.15)
Receiving aspirin	
No	1549(82.65)
Yes	325(17.35)

Table 2: Association between PN and demographic, clinical, and paraclinical characteristics of the studied patients

Variables	Patients without PN	Patients with PN	P-value	Total
Residential place				
Rural	13983(98.2)	255(1.8)	0.797	14238(100)
Urban	4351(98.2)	82(1.8)		4433(100)
Gender				
Male	8301(98.1)	161(1.9)	0.361	8462(100)
Female	10023(98.3)	176(1.7)		10199(100)
Educational level				
Illiterate	6692(97.8)	150(2.2)	0.001	6842(100)
Elementary school (one to five years learning)	4990(98.1)	97(1.9)		5087(100)
Junior school (six to nine years learning)	2293(98.5)	36(1.5)		2329(100)
High school (ten to twelve years learning)	2566(98.4)	41(1.6)		2607(100)
Academic education	1793(99.3)	13(0.7)		1806(100)
Occupation				
Governmental	691(99)	7(1)	0.032	698(100)
Self-employment	4648(98.5)	71(1.5)		4719(100)
Housewife	9292(98.2)	173(1.8)		9465(100)
Unemployed	2547(97.6)	63(2.4)		2610(100)
Retired	1156(98)	23(2)		1158(100)
Marital status			0.001	
Married	13568(98.2)	255(1.8)		13823(100)
Single	2571(99.4)	15(0.6)		2586(100)
Divorced or widow	2195(7)	67(3)		2262(100)
Smoking status				
Smoker	1848(97.8)	41(2.2)	0.208	1889(100)
Non-smoker	16486(98.2)	296(1.8)		16782(100)
Physical activity level				
Low	13305(98.1)	254(1.9)	0.720	13559(100)
Moderate	3725(98.4)	61(1.6)		3786(100)
High	790(98.4)	13(1.6)		803(100)
Very high	514(98.3)	9(1.7)		523(100)
Lipid-lowering drugs				
No	14596(98.3)	253(1.7)	0.024	14849(100)
Yes	3738(97.8)	84(2.2)		3822(100)
Type of diabetes treatment				
Oral medicines	14924(98.3)	259(1.7)	0.038	15183(100)
Oral medicines and insulin	3410(97.8)	78(2.2)		3488(100)
Receiving aspirin				
No	15388(98.3)	264(1.7)	0.006	15652(100)
Yes	2946(97.6)	73(2.4)		3019(100)

Table 3: Comparison of quantitative variables among patients with and without PN

Variable	The patients with peripheral neuropathy	The patients without peripheral neuropathy	P- value	All patients
Age	59.46±15.13	53.55±15.38	0.001	56.47±15.69
Body mass index (BMI)	27.24±4.25	26.89±4.32	0.139	26.48±4.29
Fast blood glucose (FBS)	225.12±48.6	202.41±39.82	0.001	206.22±43.11
Glycosylated hemoglobin (HBA1c)	10.55±1.78	9.17±1.59	0.001	9.77±1.65
Cholesterol	212.30±45.23	207.69±45.42	0.065	209.61±46.12
Low density lipoprotein (LDL)	132.52±35.39	128.77±37.46	0.068	131.14±38.48
High density lipoprotein (HDL)	43.70±10.68	43.81±11.42	0.875	44.31±11.82
Systolic blood pressure (SBP)	133.80±12.20	131.47±12	0.001	127.11±11.19
Diastolic blood pressure (DBP)	85.14±11.17	83.11±10.63	0.001	79.25±8.50

In the current study, it was observed that the average age in the diabetic patients who developed PN was 6 years greater than those patients without PN development. Moreover, for each year of increase in age of patients, the HR occurrence of PN will increase by 2%[18]. In other studies carried out around the world, the same results were obtained. In a study by Barbosa *et al.* on the patients with PN in Portugal, it was observed that on average, the mean age of patients with PN was 5.7 years greater than those patients without PN[19]. Therefore, by raising the age, the risk of PN is increased in diabetic patients.

Moreover, in the current study, the adjusted HR of the PN in men was equal to 3.66 (95% CI: 1.15-11.67). In a study by Booya *et al.* with the purpose of examining the factors affecting the incidence of diabetic-associated PN, the adjusted odds ratio of PN in men was equal to 2.9[18]. These results are consistent with the findings of the DCCT study (diabetes control and complications trial study)[20].However, in some studies, the female gender was introduced as the predictive factor for incidence of PN in diabetic patients[21,22]. Nonetheless, in some studies, no significant statistical relation was observed between gender and risk of developing PN[23,24].

In the present study, it was also observed that the type of diabetes treatment affects the occurrence of PN. The incidence rate of PN in patients who simultaneously received oral medicines and insulin therapeutic regimen was greater than those in other groups; therefore, in comparison to the oral treatment group, the un-adjusted HR of PN was equal to 1.29 (95% CI: 1.02-1.66). In a study by Marvasti *et al.*, it was observed that compared to the oral treatment group, the HR of PN in the insulin-treated group was equal to 1.42 and in the group of insulin and oral treatment, it was equal to 1.41[25].

In the present study, it was observed that increasing the follow-up duration of the Type 2 diabetes patients led to an increase in the HR of PN occurrence. Such results were observed in other studies[23,24,26]. In a study by Booya *et al*, it was observed that for each 1-year increase of patient follow-up period, the HR of PN occurrence will increase by 10%[18]. Nonetheless, in some studies, no significant statistical relations were observed between the duration of diabetes and incidence of PN[27,28].

Furthermore, in our study, it was observed that the average of HBA1c in patients with PN was equal to 10.55% and in patients without the symptoms of PN, it was 9.17%; this difference was statistically significant ($p \leq 0.001$). Moreover, the un-adjusted HR of PN increased 10% per one percent increase in HBA1c. The relation between HBA1c and complications of Macrovascular (Heart disease)-related diabetes, and Microvascular diabetes (including peripheral neuropathy, retinopathy, and nephropathy) have been demonstrated in numerous studies[29,30]. In the prospective study in Britain in which the diabetes patients were followed up for an average of 10 years, it was observed that per 1% increase in level of HBA1c, the complications of diabetes increased by 37%[31]. In this study, no significant statistical relation was observed between smoking, hypertension and hyperlipidemia, and development of peripheral neuropathy; similar results were observed in the study by Booya *et al*[18].

There were some limitations, including the time when there was no record or the information was incomplete regarding some medical cases, in which case

Table 4: The incidence rate of PN based on the demographic, clinical and Paraclinical characteristics of the studied patients

Variables	Number of PN	Follow up(per 1000 person-years)	Incidence rate(95% Confidence interval)
Gender			
Male	161	4.2462	37.91(32.49-44.25)
Female	176	5.0852	34.61(29.85-40.12)
Residential place			
Urban	82	2.2211	36.91(29.73-45.83)
Rural	255	7.1102	35.86(31.72-40.54)
Age			
43 and lower	58	2.5547	22.70(17.55-29.36)
44-55	69	2.3060	29.92(23.63-37.88)
56-67	82	2.4595	33.34(26.85-41.39)
67 and higher	128	2.0111	63.64(53.52-75.68)
Occupation			
Retired	23	0.5965	38.56(25.62-58.02)
Government job	7	0.3541	19.76(9.42-41.46)
Non-government job	71	2.3634	30.04(23.80-37.90)
Housewife	173	4.7123	36.71(31.62-42.61)
Unemployed	63	1.3051	48.27(37.71-61.79)
Educational level			
Illiterate	150	3.4279	43.75(37.28-51.35)
Elementary school	97	2.5271	38.38(31.45-46.83)
Junior school	36	1.1739	30.66(22.12-42.51)
High school	41	1.3042	31.43(23.14-42.69)
Academic education	13	0.8983	14.47(8.40-24.92)
Marital status			
Single	15	1.2834	11.68(7.014-19.38)
Married	255	6.9149	36.87(32.61-41.69)
Divorced & Wife died	67	1.1330	59.13(46.54-75.13)
Smoking status			
Non-smoker	296	8.3742	35.34(31.54-39.61)
Smoker	41	0.9572	42.83(31.53-58.17)
Diabetes therapy			
Oral medicines	259	7.5324	34.38(30.44-38.83)
Oral medicines and insulin	78	1.7989	43.35(34.72-54.13)
Physical activity			
Low	254	6.7783	37.47(33.13-42.37)
Moderate	61	1.8990	32.12(24.99-41.28)
High	13	0.3990	32.58(18.91-56.10)
Very high	9	0.2550	35.29(18.36-67.83)
BMI			
Normal	103	3.2310	31.87(26.28-38.67)
Overweight	151	3.9484	38.24(32.60-44.85)
Obesity	83	2.1520	38.56(31.10-47.83)

Table 5: The un-adjusted HR of PN based on the demographic, clinical and Paraclinical characteristics of the studied patients

Components of variable	Hazard ratio	P-value
Residency place		
Rural	0.96(0.75-1.23)	0.788
Urban	1	-
Gender		
Male	1.09(0.88-1.35)	0.409
Female	1	-
Education		
Illiterate	3.02(1.71-5.32)	0.001
Elementary school (one to five years learning)	2.64(1.48-4.71)	0.001
Junior school (six to nine years learning)	2.11(1.12-3.98)	0.021
High school (ten to twelve years learning)	2.16(1.15-4.03)	0.016
Academic education	1	-
Occupation		
Governmental	1	
Retired	1.95(0.83-4.55)	0.120
Self-employment	1.50(0.69-3.27)	0.302
Housewife	1.83(0.86-3.90)	0.116
Unemployed	2.42(1.11-5.29)	0.026
Marital status		
Married	3.14(1.86-5.29)	0.001
Single	1	
Divorced & Wife died	5.03(2.87-8.80)	0.001
Smoking status		
Positive	1.21(0.87-1.68)	0.246
Negative	1	-
Physical activity status		
Low	1	-
Moderate	0.85(0.64-1.13)	0.283
High	0.86(0.49-1.50)	0.603
Very high	0.92(0.47-1.78)	0.807
Blood anti-lipid drugs		
No	1	-
Yes	1.28(1.03-1.64)	0.034
Diabetes therapy		
Oral medicines	1	-
Oral medicines and insulin	1.29(1.02-1.66)	0.036
Aspirin reception		
Yes	1.43(1.10-1.86)	0.006
No	1	
Age	1.025(1.017-1.033)	0.001
BMI	1.019(0.994-1.044)	0.128
FBS	1.02(1.01-1.03)	0.001
HBA1c	1.10(1.04-1.16)	0.001
Cholesterol	1.002(0.999-1.004)	0.066
LDL	1.002(0.999-1.005)	0.071
HDL	0.999(0.989-1.008)	0.871
SBP	1.014(1.006-1.023)	0.001
DBP	1.016(1.007-1.026)	0.001
Studying period	1.16(1.14-1.18)	0.001

Table 6: The adjusted HR of PN based on the demographic, clinical and Paraclinical characteristics of the studied patients

Components of variable	Hazard ratio	P-value
Gender		
Male	3.66(1.15-11.67)	0.028
Female	1	
Age	1.020(1.009-1.06)	0.001
Occupation		
Governmental	1	
Retired	1.65(0.69-3.94)	0.254
Self-employment	1.56(0.71-3.43)	0.268
Housewife	4.09(1.02-16.38)	0.046
Unemployed	2.08(0.93-4.67)	0.074
Education		
Illiterate	1.73(0.94-3.17)	0.076
Elementary school (one to five years learning)	1.86(1.01-3.47)	0.048
Junior school (six to nine years learning)	1.90(0.96-3.72)	0.062
High school (ten to twelve years learning)	2.37(1.22-4.60)	0.011
Academic education	1	
Marital status		
Single	1	
Married	2.18(1.24-3.83)	0.007
Divorced & Wife died	3.02(1.61-5.65)	0.001
BMI	1.03(1-1.06)	0.032
Studying period	1.19(1.17-1.22)	0.001

the information was then completed through contacting the patient to provide information on the missing variables. Furthermore, this research study only investigated patients with active medical files in health centers, houses, or diabetes units.

CONCLUSIONS

The maximum rates of PN incidence were observed in men, urban patients, and patients with oral medicines and insulin therapeutic regimens, as well as patients who were overweight or obese and those with low physical activity. In addition, the adjusted HR of PN in men, housewives, divorced or wife died patients, and people with high school education level were higher than the others. Thus, training, screening and diagnostic programs should be conducted with more sensitivity and accuracy in patients who are at greater risk of PN. Furthermore, in order to identify the complications in the initial steps of the disease as well, based on the data in this study, it is advisable to initiate effective and proper therapeutic actions in order to prevent greater complications, and to improve the quality of life in diabetic patients.

ETHICAL CONSIDERATIONS

This article was extracted from the Ph.D. thesis of Abdollah Mohammadian-Hafshejani from Tehran University of Medical Sciences with the following code: 9221128003. In this study, there was no intervention, nor was any personal information exclusively studied. Furthermore, in order to respect individual privacy, no full names or other private details were included in the checklist of the data collection. All patient information were included in the checklist as codes (including the codes of health centers and patients).

COMPETING INTERESTS

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

AMH and MAM: initial conception and design of the study. **AMH, RM, NM and MAM**: critical revision of article. All authors have read and approved the final manuscript.

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ABBREVIATIONS

BMI: Body mass index
DBP: Diastolic blood pressure
FBS: Fast blood glucose
HBA1c: Glycosylated hemoglobin
HDL: High density lipoprotein
LDL: Low density lipoprotein
PN: Peripheral neuropathy
SBP: Systolic blood pressure

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