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

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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)⁴. 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 2030⁵. Peripheral neuropathy (PN) is among the most prevalent complications of diabetes that can lead to impaired mobility of patients with diabetes⁶,⁷. 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%⁸. PN involves about 37% of patients with type 1 diabetes, and at least 20-40% of patients with type 2 diabetes⁹. The prevalence of PN was equivalent to 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

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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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. 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.

**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 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<0.001) and have higher BMI (p=0.139), FBS (p<0.001), HBA1c (p<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 medicine regimen and insulin therapeutic regimen, 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, 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 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%. In a study carried out by Lloyd 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%. Similarly, in a study by Sands et al., after 5-year follow-up of patients it was 28.6%.
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**                     |                     |                  | 0.208   |           |
| Smoker                                 | 1848(97.8)          | 41(2.2)          |         | 1889(100) |
| Non-smoker                             | 16486(98.2)         | 296(1.8)         |         | 16782(100)|
| **Physical activity level**            |                     |                  | 0.720   |           |
| Low                                    | 13305(98.1)         | 254(1.9)         |         | 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**               |                     |                  | 0.024   |           |
| No                                     | 14596(98.3)         | 253(1.7)         |         | 14849(100)|
| Yes                                    | 3738(97.8)          | 84(2.2)          |         | 3822(100) |
| **Type of diabetes treatment**         |                     |                  | 0.038   |           |
| Oral medicines                         | 14924(98.3)         | 259(1.7)         |         | 15183(100)|
| Oral medicines and insulin             | 3410(97.8)          | 78(2.2)          |         | 3488(100) |
| **Receiving aspirin**                  |                     |                  | 0.006   |           |
| No                                     | 15388(98.3)         | 264(1.7)         |         | 15652(100)|
| Yes                                    | 2946(97.6)          | 73(2.4)          |         | 3019(100) |
The patients with peripheral neuropathy (PN) were compared to those without PN based on several variables (Table 3). The analysis revealed that the patients with PN had significantly higher levels of fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), and cholesterol compared to those without PN. Moreover, the incidence rate of PN in patients who simultaneously received oral medicines and insulin treatment was greater than those in other groups. Furthermore, in comparison to the oral treatment group, the adjusted HR of PN in the insulin-treated group was equal to 3.66 (95% CI: 1.15-11.67). 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%. Nonetheless, in some studies, no significant statistical relations were observed between the duration of diabetes and incidence of PN.

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% (p=0.001). 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. Therefore, by raising the age, the risk of PN is increased in diabetic patients.

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. However, in some studies, no significant statistical relations were observed between the duration of diabetes and incidence of PN. 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 ≤ 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. 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%. 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.

There were some limitations, including the time when there was no record or the information was incomplete regarding some medical cases, in which case
| 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)                      |
| 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  
BMI: Body mass index  
P: Peripheral neuropathy  
SBP: Systolic blood pressure  
SPONSORSHIP

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