

## Survey of Effective Factors in the Event of Neuropathy in Type 2 Diabetic Patients

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### Abstract

**Introduction:** Diabetic neuropathy is a common and severe complication of diabetes that its progression can lead to disability and even amputation in diabetic patients. The aim of this study was to determine the effective factors in the event of neuropathy and to assess the cumulative incidence of neuropathy in patients with type 2 diabetes.

**Methods:** In this cohort study, all patients with type 2 diabetes who were registered at Fereydunshahr Diabetes Clinic, Isfahan, Iran, were selected by census method. They were followed up for diagnosis of neuropathy since 2006 until March 2016. To investigate the quantitative and qualitative effective factors in the event of neuropathy, one-sample t-test and chi-square test, respectively, were used. And for modeling of effective factors in the event of neuropathy, logistic regression was used. All statistics were analyzed by R software (version 3.2.3) and P values less than 0.05 were considered significant.

**Results:** At the end of 10-year follow-up, cumulative incidence and prevalence of neuropathy were estimated 31% and 41.6%, respectively. After removal of confounders in the final model, variables such as age, ethnicity, family history of diabetes, duration of diabetes, FBS and HDL levels were identified as effective factors in the event of neuropathy ( $P < 0.05$ ).

**Conclusion:** Low levels of HDL and poor control of FBS level are modifiable risk factors for diabetic neuropathy. But non-modifiable risk factors include Persian ethnicity, family history of diabetes, age and increase of diabetes duration. For this reason, in order to increase the HDL level and to decrease FBS level, education is recommended particularly in elderly patients with a family history of diabetes.

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### Introduction

Diabetes is a complex and common metabolic disorder that is associated with chronically high blood sugar and fat, carbohydrates and proteins metabolism disorders. Diabetic

neuropathy is a common complication of diabetes that can cause disability in diabetic patients (1).

Peripheral neuropathy (PN) affects at least 20 to 40% of the patients with type 2 diabetes and

approximately 37% of the patients over 18 years old with type 1 diabetes (2). The prevalence of diabetic peripheral neuropathy (DPN) has reported 28% in Europe (3), 34% in the study of Asian Diabetes Care at 230 Diabetes Care Centers in 12 countries (4), and 75.1% in Isfahan, Iran (5). However, it seems that one in three diabetic patients suffers from neuropathy (6).

This study aimed to determine the effective factors in the event of neuropathy in patients with type 2 diabetes.

### Materials and Methods

In this cohort study, data were collected by census method from all patients with type 2 diabetes in Fereydunshahr, Isfahan, Iran. For this purpose, a sample of 440 patients (306 females and 134 males) with type 2 diabetes was followed up since March 2006 until March 2016 for diagnosis of neuropathy.

There are various methods for diagnosis of peripheral neuropathy, such as nerve conduction velocity (NCV) or vibration perception threshold testing as qualitative methods or valid questionnaires such as United Kingdom screening test (UKST), which is a simple, subjective and symptom-based instrument about sensory symptoms of neuropathy or, Michigan Neuropathy Screening Instrument (MNSI); but according to the findings resulted from patients examination, the precision of each method at neuropathy diagnosis in diabetic and non-diabetic patients is different (7). In this study, regardless of the precision of these methods, the effective factors in the event of neuropathy in patients with type 2 diabetes, using Michigan's questionnaire together with

monofilament tests were evaluated. Tabatabaei suggested the simultaneous use of Michigan questionnaires and monofilament tests for diagnosis of diabetic neuropathy (8).

In terms of moral considerations, the names of all patients who participated in the study were confidentially protected and entered by the code into the software. This study was approved by the Ethics Committee of Iran University of Medical Sciences (code: 27445) in January 2016. Nevertheless, all relevant licenses were taken from Fereydunshahr Health Center officials.

### Results

From 440 patients with type 2 diabetes, 134 patients were male (30.5%) and 306 female (69.5%). The mean age of the patients, was 64.4 ( $1.15 \pm$ ) years, the median age was 64.5 with standard deviation of 11.15 and the age range of the patients was 31 to 95 years. Also, the mean duration of diabetes in patients was 114.9 ( $6.92 \pm$ ) months, the median duration of diabetes was 103.7 months with standard deviation of 11.15 and the minimum and maximum duration of this disease, were 3 and 462 months, respectively.

In this study, 7.3% of the patients ( $n= 32$ ) were withdrawn from the study, because event of neuropathy in these patients was unclear. The prevalence of neuropathy in patients with type 2 diabetes in Fereydunshahr was 41.6% (183 patients) in 2006. At the end of 10 years of study, 30.7% of the patients (114 patients) suffered from neuropathy (cumulative incidence).

**Table 1.** The final model of the effective factors in the event of neuropathy, a logistic regression analysis (P<0.05)

Variable	P-value	Odds Ratio	CI 95%		$\beta$	S.E.	
Age	< 50 years	0.021	Reference Group				
	50 to 59 years	0.166	1.97	0.76	5.13	0.68	0.489
	60 to 69 years	0.008	3.44	1.38	8.55	1.24	0.465
	$\geq$ 70 years	0.011	3.48	1.33	9.17	1.25	0.492
Ethnicity	Georgian	0.048	Reference Group				
	Bakhtiari	0.300	1.40	0.74	2.63	0.335	0.323
	Turk	0.081	2.33	0.90	6.02	0.846	0.484
Family history of diabetes	Fars	0.010	2.49	1.25	4.98	0.911	0.353
	Yes	0.006	Reference Group				
No	2.12		1.24	3.61	0.75	0.272	
Duration of diabetes	< 36 months	0.003	Reference Group				
	36 to 72 months	0.001	5.75	2.04	16.13	1.75	0.529
	72 to 108 months	0.068	2.75	0.93	8.13	1.01	0.554
FBS	> 108	0.046	3.07	1.02	9.26	1.12	0.563
	< 140	0.029	Reference Group				
$\geq$ 140	1.82		1.06	3.13	0.60	0.276	
HDL	< 55	0.005	Reference Group				
	$\geq$ 55		3.46	1.45	8.22	1.24	0.442

Significant variables in the univariate analysis (P<0.20), were nominated for entry into the logistic regression analysis. In the final model, and after removal of confounders in the final model, variables such as age, ethnicity, family history of diabetes, duration of diabetes, FBS, and HDL level, were identified as the major effective factors in the incidence of neuropathy (Table 1).

## Discussion

In this study, the prevalence of neuropathy in patients with type 2 diabetes was estimated 41.6% in Fereyduhshahr, which is consistent with the findings of other studies in Iran and the World. The prevalence of neuropathy in patients with type 2 diabetes in Muller's study was estimated 20 to 40% (2), in the Diabcare-Asia, 34% (4), and in meta-analysis by Sobhani et al. in Iran, 53% (9).

In this study, the risk of neuropathy (cumulative incidence) was estimated 30.7%, after 10 years of follow-up. The cumulative incidence of neuropathy in the Europe diabetes study with a 7-year follow-up was 23.5% (10), in Pittsburgh study with two follow-up intervals; 4-year (11) and 10-year (12), 13% and 34.2%, respectively, and in San-Luis study with 5-year follow-up was 28.6% (13). These results show that the cumulative incidence of neuropathy increases with increase of the follow-up duration.

Family history of diabetes, was one of the most important known risk factors in this study (P<0.001, OR=2.07). The proportion of neuropathy in patients with a family history of diabetes was more than those without a family history of diabetes (approximately 52% vs 34%), which is confirmed by the other studies (15). According to the above mentioned results, it can be suggested that genetic agents are likely to play a key role in the development of neuropathy (18). Some

studies insisted on the role of genetic agents (VEGF gene polymorphism) in the evolution of neuropathy (19).

In this study, according to the chi-square test, there is significant relationship between HDL less than 55 mg/dL and neuropathy ( $P=0.017$ ,  $OR=2.36$ ). Also, according to the final regression model, the odds of neuropathy in patients who had HDL levels less than 55 mg/dL, is 3.46 times more than the other group ( $P=0.005$ ). Also, the proportion of neuropathy event in people with high HDL levels, was more than the other groups (approximately 46% vs 26%), which is consistent with the results of Other studies (10, 14).

The other known risk factor in this study, was longer duration of diabetes ( $P<0.001$ ) that in many studies have been also mentioned as a risk factor (14-16). However, in few studies, the relationship between duration of diabetes and neuropathy was not significant (17). In this study, along with increase of diabetes duration, neuropathy has also increased, as 60.6% of patients who had diabetes more than 9 years, suffered from neuropathy, while this proportion in diabetic patients who had diabetes less than 3 years, was 15.9%. Also, a significant relationship between age and occurrence of neuropathy in neuropathic and non-neuropathic patients was observed ( $P=0.030$ ) (Table 1).

In this survey, the odds of neuropathy in patients with FBS higher than 140 mg/dL, was 1.82 times more than those with FBS less than 140 mg/dL ( $P=0.029$ ). Nearly half of the neuropathic patients (49.2%), had

FBS more than 140 mg/dL, as a result, this variable is determined as an important risk factor in the development of neuropathy ( $P<0.001$ ,  $OR=2.09$ ). Several studies have predicted FBS increase as an effective factor in the event of neuropathy (14).

Diagnosis of neuropathy in the Fars ethnicity was more than the other ethnicities who are living in Fereydunshahr ( $P=0.007$ ). One of the main reasons for this may be attributed to their dietary habits (eating more sweetmeat). For example, the majority of bakeries, confectioneries and pastries in township belong to the Fars ethnicity. Only two studies has been done on the relationship between neuropathy and ethnicity by author in Iran (20, 21).

## Conclusion

Along with increase of diabetes duration, neuropathy also increases in diabetic patients. With control of blood glucose level and education about diet and its observance, specially in high-risk groups (such as elderly patients, women, patients with low HDL levels, and those with a family history of diabetes), the occurrence of neuropathy will be delayed and their quality of life will be improved.

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