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**Original Article**

# Risk Factors Associated with Diabetic Peripheral Neuropathy in Non-insulin Dependent Diabetes Mellitus at a Tertiary Care Hospital in Peshawar, Pakistan; An Analytical Cross Sectional Study

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## Abstract

**Objective:** To identify the risk factors associated with diabetic peripheral neuropathy (DPN) in patients with non-insulin dependent diabetes mellitus (NIDDM) at a tertiary care hospital of an underdeveloped country.
**Study type, settings & duration:** This cross sectional analytical study was conducted over a period of one year at Khyber Teaching Hospital, Peshawar from January to December 2013.
**Methodology:** Participants with diabetes mellitus (DM) satisfying the inclusion criteria were enrolled in the study and categorized into two groups, one having DPN(n=110) and the other having no DPN(n=110) based on modified Neuropathy Disability Score (mNDS). Socio-demographic characteristics and disease profile of the participants were taken with structured interview questionnaire and analysed using STATA SE 13.
**Results:** The overall response rate was 92.4% (n=220) and mean age was 54.5±8.8 years with equal male to female ratio. Participants with DPN had significantly higher disease duration (>10 years: 60% v 18.2%, p<0.001), poorer glycaemic control (HbA1c 8.0-10.0 = 36.4% v 26.4%, HbA1c>10.0 = 28.2% v 10.0%, p<0.001),raised uric acid (14.5% v 4.6%, *p* <0.02) hypertension (69.1% v 53.6%, *p*=0.02), central obesity (72.7% v 47.3%, *p* <0.001) and overweight/obese status (BMI 25.0-29.9=52.7% v 29.1%, BMI ≥30.0= 22.7% v 8.2%, *p* <0.001).Also the combination of insulin and oral hypoglycaemic drugs were significantly associated with DPN as against to oral hypoglycaemic drugs alone. There was no difference in the two groups with respect to age, sex, monthly income, smoking status, alcohol use or the presence of dyslipidaemia.
**Conclusion:** Amongst the various risk factors, higher duration of DM, poor glycaemic control and raised BMI are strongly associated with DPN.
**Key words:** Diabetic peripheral neuropathy, modified neuropathy disability score, HbA1c, body mass index, dyslipidaemia, hypertension.

## Introduction

Diabetic peripheral neuropathy (DPN) is one of the major disabling micro-vascular complications of diabetes mellitus(DM) , and greatly contributes to morbidity and mortality in terms of pain, loss of mobility, foot ulceration, foot/limb amputation and death.[1] It has been estimated that up to 70% of non-traumatic lower limb amputations are directly related to DPN, with up to 85% of such amputations being preceded by foot ulceration.[2] Disease prognosis among patients with DPN is poor, with mortality as high as 47.6 % at first year and up to an alarming 70.6% at 5 years of limb amputation.[3]

The prevalence of DPN in the diabetic population worldwide is significantly high, and estimates suggest that up to one third of all diabetics may suffer from DPN.[4] The occurrence is found to vary widely with the geographic and socio-demographic profile of the studied populations. DPN in developed countries such as UK and the United states stands at around 28.5%, whereas in

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**Authors Contribution**

IG conceptualized the project. IG & TG did the data collection. IG & MFS performed the statistical analysis. Literature search, drafting, revision & writing of manuscript were done by IG, MFS & TG.

developing countries the proportion is slightly higher. Regionally, Pakistan has the second highest prevalence of DPN (39.6%) after Iran (45.7%). In India, DPN in adult diabetics stands at 18.8%. There is no single aetiology for DPN and current literature suggests several independent risk factors which may include age, patient's height, duration of diabetes, poor glycaemic control, presence of dyslipidaemia and hypertension responsible for DPN as demonstrated in various populations.[5-7] The development of DPN predisposes the diabetic individuals to several complications such as depression, foot and ankle fractures, foot ulcers, infections, gangrene and lower limb amputations which further affect disease prognosis.[2,8] In Pakistan, there is limited scientific evidence on peripheral neurological disorders associated with diabetes despite a very high prevalence of diabetes and its sequelae. The unavailability of properly conducted studies and non-uniform distribution of risk factors across populations make it crucial to understand the development of peripheral neuropathy in our setting. Based on the above rationale, we conducted this study to identify the risk factors associated with diabetic peripheral neuropathy in adult patients with non-insulin dependent diabetes mellitus in a tertiary care hospital setting of Pakistan.

## Methodology

This cross sectional analytical study was conducted over a period of one year at Khyber Teaching Hospital Peshawar.

We included participants who satisfied the following criteria: adult patients aged >18 years, either gender, having been diagnosed with NIDDM and admitted to the health care facility for any medical reason from January to December 2013. Participants were excluded if the modified neuropathy disability score (mNDS) could not be applied (participants being critically ill or having had single or dual lower limb amputations. We also excluded participants with CKD, underlying heart or liver failure (independent risk factors for neuropathy), or if they reported use of vitamin supplements or drugs for the treatment of any neuropathies.

Participants were recruited in the study from inpatient medical wards, using a non-probability, purposive sampling approach. Patients were assessed by the research assistant and their eligibility was based on the mentioned criteria. Eligible patients were explained purpose and procedure of the study and written informed consent was obtained from those who agreed to participate in the study. After obtaining a written, informed consent, the participants were referred to the study physicians for data collection and physical examination.

Data was collected using a structured interview questionnaire which was administered face to face by two trained general physicians. The interview questionnaire elicited information on socio-demographic characteristics and disease profile of the participants which included age (years), gender (male/female), height (cm) and weight (kg), marital status (single/married/separated/divorced), monthly income (rupees), duration of diabetes (<5, 5-10, > 10 years), smoking (yes/no), type of treatment (oral hypoglycaemic drugs/insulin/combination) and waist circumference (cm). Diagnosis of Diabetes mellitus was defined as per the American Diabetes Association criteria.[9] Body mass index was calculated from height and weight by the formula: Weight (kg) / Height $(m)^2$and classified into three categories (<25 $kg/m^2$, 25-30 $kg/m^2$, >30$kg/m^2$). Hypertension was defined as blood pressure of 140/90 mmHg or higher, measured around the patients right arm with appropriate sized mercury sphygmomanometer, by trained physician on at least two separate occasions or if the patient was already taking antihypertensive medications. Smoking was defined as having smoked at least one cigarette a day for the last six months. Central obesity was defined as waist circumference of more than 86 cm for females and more than 90 cm for males as are specified for Asian population.[10] Monthly income was based upon the World Bank Group's mission 2011 report for the definition of poverty line.

Diabetic peripheral neuropathy: DPN was diagnosed on the basis of modified Neuropathy Disability score.[11] Four parameters were assessed including pin prick sensation (using Neurotip), temperature sensation (using warm and cool rods), vibration sensation (using 128 Hz tuning fork) and Achilles tendon reflex (using tendon hammer). A score of 6 or more than 6 out of 10 was taken positive for DPN.[11]

Blood samples for fasting lipid profile and HbA1c were obtained from all participants on the next morning after enrolment into the study. The patients fasted for 12 hours before taking the blood sample which was immediately sent to hospital laboratory. Enzymatic method was used to measure the concentration of total cholesterol, HDL cholesterol and triglyceride level (Lab Corp, Raritan, NJ). LDL cholesterol was calculated using Friedewald equation. For triglyceride level higher than 400 mg/dl, LDL cholesterol was measured directly. Dyslipidaemia was defined according to

National Cholesterol Education Program Adult Treatment Panel III.[12] HbA1c level was also measured by high performance liquid chromatography (HPLC) method and was used for the assessment of glycaemic control. It was further categorized into (1) less than 7% (2) 7-7.9% (3) 8-10% and (4) more than 10%.

Separate random sample was taken for serum uric acid level. Normal serum urate level was taken as 2-7 mg/dl for male and 2-6 mg/dl for female. A single 24 hours urinary sample was collected in a clean graduated jar and was sent to laboratory for assessment of nephropathy which was defined as a positive dipstick test of 24 hours urinary protein excretion more than 299mg/d.[13]

All data were analysed using STATA SE 13. Descriptive statistics were calculated for all the variables in the study. Means with standard deviations were calculated for continuous variables whereas proportions were calculated for categorical variables. Inferential statistics were based on calculation of prevalence ratios obtained using the Cox proportional hazards algorithm.At the bivariate level, unadjusted prevalence ratios and their 95% confidence intervals were obtained for all the variables in the study. Age and height were recorded as quantitative data, and were retained as continuous following scale examination.We used a purposive, step-wise modelling approach to obtain adjusted prevalence ratios and their 95% confidence interval in order to identify independent risk factors for diabetic peripheral neuropathy. Variables which were significant at the bi-variate level were retained on the basis of the partial log likelihood test. A *p*-value <0.05 was considered statistically significant at the multivariate level.The final model was checked for outlying or influential observations and was reported with the overall log likelihood.

The Ethical approval was obtained from Department Review Committee of Khyber Teaching Hospital, Peshawar.

## Results

A total of 250 adult males and females with type 2 diabetes mellitus admitted to Khyber Teaching Hospital, Peshawar were screened for inclusion. A total of 12 patients were excluded due to ineligibility; written informed consent was obtained from 220 participants (response rate: 92.4%). The final analysis was done on 110 patients each with and without DPN (Figure-1). The mean age of the overall sample was 54.5±8.8 years with an equal representation of males and females. Common co-morbid conditions included hypertension (61%), dyslipidaemia (58.6%), raised BMI (56%) and central obesity (60%). About 39 participants (17.7%) were identified as smokers with a median smoking duration of 10 pack years. Total of 22.3% were also diagnosed with diabetic nephropathy. Overall, control of diabetes was poor in both groups with only 25.9% having HbA1c below 7.0%. Participants' socio-demographic and health characteristics stratified by the presence of DPN are presented in Table-1.

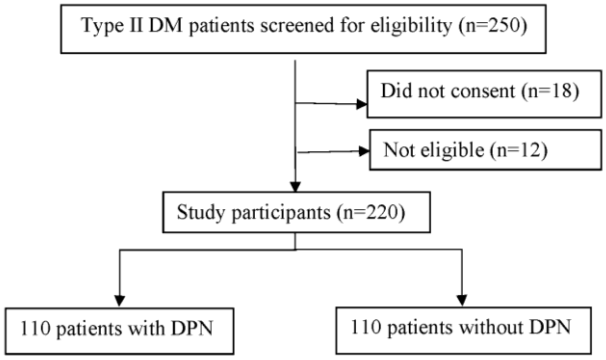


**Figure1: Flow diagram for the selection of type 2 diabetes mellitus patients with and without DPN.**

**Table 1: Demographic characteristics of type 2 diabetes patients with and without diagnosis of diabetic peripheral neuropathy. (n= 220)**

| | *DPN + n (%)* | *DPN – n (%)* | *p-value* |
|---|---|---|---|
| Age* | 54.7±9.1 | 54.3±8.6 | 0.74 |
| Male | 52 (47.3) | 58 (52.7) | 0.41 |
| Smoking | 20 (18.2) | 19 (17.3) | 0.86 |
| Hypertension | 76 (69.1) | 59 (53.6) | 0.01 |
| Dyslipidaemia | 60 (54.5) | 69 (62.7) | 0.21 |
| Central obesity | 80 (72.7) | 52 (47.3) | <0.01 |
| Alcohol consumption | 3 (2.7) | 1 (0.9) | 0.31 |
| Diabetic nephropathy | 34 (30.9) | 15 (13.6) | 0.02 |
| Hyperuricemia | 32 (14.4) | 10.1 (4.6) | 0.02 |
| Body mass index | | | |
| normal(<25 kg/m$^2$) | 27 (24.5) | 69 (62.7) | <0.001 |
| overweight (25-30 kg/m$^2$) | 58 (52.7) | 32 (29.1) | |
| obese (>30 kg/m$^2$) | 25 (22.7) | 9 (8.2) | |
| Monthly income <5000 rupees | 61 (55.4) | 58 (52.7) | 0.68 |

*in years, mean±SD

Bi-variate analysis suggested no differences in the two groups with respect to age, sex, monthly income, smoking status, alcohol use or the presence of dyslipidaemia. However participants with DPN had significantly higher disease duration than those without DPN (>10 years: 60% with DPN vs 18.2% without DPN, *p* <0.001) (Figure-2) and poorer glycaemic control than those without DPN, (HbA1c 8.0-10.0= 36.4% with DPN vs 26.4% without DPN, *p* <0.001), (HbA1c >10.0= 28.2% with

DPN vs 10.0% without DPN, *p* <0.001) (Figure-3). The two groups also significantly differed by treatment as for example, amongst patients on oral hypoglycaemic drugs (46.4% were having DPN vs 77.3% without DPN, *p* <0.001) whereas amongst patients on combination therapy of insulin and oral hypoglycaemic drugs, (56.0% were having DPN vs 20.0% without DPD, *p* <0.001) (Figure-4).

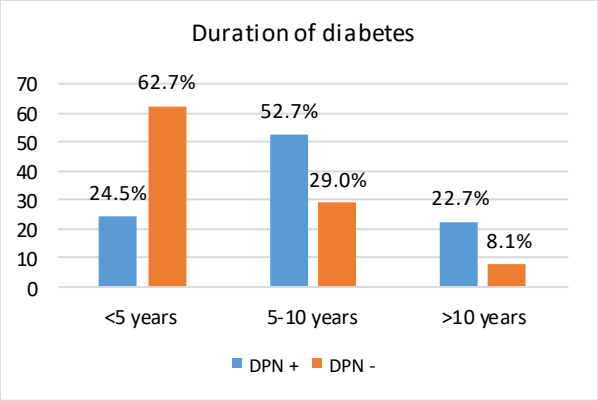


**Figure 2: Diabetes duration of study participants, stratified by the presence of diabetic peripheral neuropathy. (n=220)**

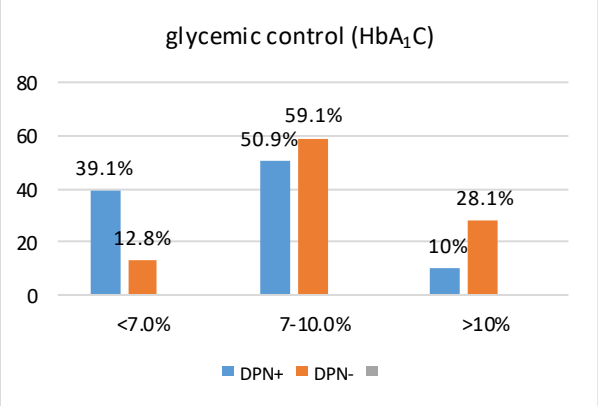


**Figure 3: Glycaemic control of study participants, stratified by presence of diabetic peripheral neuropathy. (n=220)**

In addition, we also found DPN patients to have higher proportions of raised uric acid, (14.5% with DPN vs 4.6% without DPN, *p* <0.02), hypertension (69.1% with DPN vs 53.6% without DPN, *p* =0.02), central obesity (72.7% with DPN vs 47.3% without DPN, *p* <0.001) and overweight/obese status (BMI 25.0-29.9=52.7% with DPN vs 29.1% without DPN, BMI > 30.0= 22.7% with DPN vs 8.2% without DPN, *p* <0.001). Based on a step-wise logistic regression approach, we identified two parameters i.e. prolonged duration of diabetes, & progressively poorer glycaemic control as key predictors of DPN while controlling for the effect of BMI, which was marginally significant and retained for its biologic importance. Thus the adjusted prevalence of DPN was found to be 2.2 (95% CI: 1.25-3.92) times higher in individuals with a prolonged duration of diabetes (>5 years) compared to individuals with duration <5 years, and 1.7 (95% CI: 1.11-2.85) to 1.9 (95% CI: 1.12-3.43) times higher in overweight and obese individuals respectively as compared to individuals with a normal BMI. The results of multivariable analysis presenting crude and adjusted prevalence ratios is presented as Table-2.

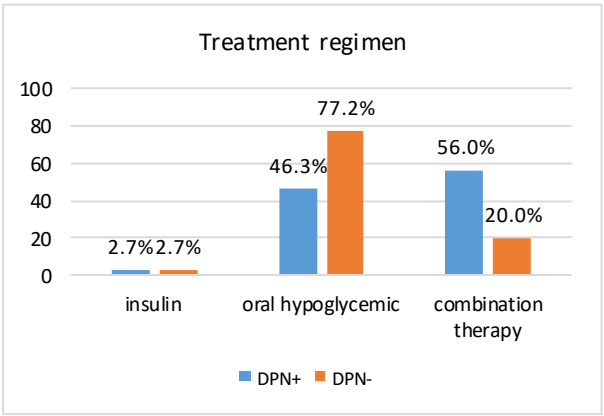


**Figure 4: Treatment regimen of study participants, stratified by presence of diabetic peripheral neuropathy. (n=220)**

**Table 2: Results of multivariable logistic regression showing crude and adjusted prevalence ratios for factors associated with diabetic peripheral neuropathy in type 2 diabetes. (n=220)**

| | *Prevalence Ratios* | | | |
|---|---|---|---|---|
| | *Crude* | *95% CI* | *Adjusted* | *95% CI* |
| *Duration of Diabetes** | | | | |
| <5 years | 1 | - | 1 | - |
| >5 years | 3.1 | 1.86-5.37 | 2.2 | 1.25-3.92 |
| *BMI* | | | | |
| Normal (<25 kg/m$^2$) | 1 | - | 1 | - |
| Overweight (25-30 kg/m$^2$) | 2.3 | 1.46-3.65 | 1.4 | 0.78-2.63 |
| Obese (>30 kg/m$^2$) | 2.7 | 1.57-4.68 | 1.8 | 0.933-3.52 |
| *HbA1c** | | | | |
| <7% | 1 | - | 1 | - |
| 7-10% | 2.1 | 1.22-3.89 | 1.7 | 1.11-2.85 |
| >10% | 3.0 | 1.59-5.64 | 1.9 | 1.12-3.43 |

* *p*-value <0.05, Log likelihood = -575.60

## Discussion

Our study adds new evidence to diabetes research in the local populace. We identified three key risk factors (higher duration of DM, poor glycaemic control and raised BMI) to be associated with diabetic peripheral neuropathy in our population.

Previous studies from other areas have highlighted several risk factors to be associated with DPN in adult type 2 diabetes.[5,7,14] In our study, diabetes duration was the strongest predictor of DPN with 2.2 time greater prevalence of DPN among patients with a greater disease duration (>5 years). Our results are comparable to previous research in Iran and Bangladesh which have demonstrated 5-7% increase in odds of DPN each year among adult diabetics.[15,16] Boru and colleagues,[17] have similarly demonstrated a persistent increase in odds of DPN for every 5 years increase in total duration, with subjects >20 years having highest odds of up to 2.9. As a non-modifiable risk factor, need for optimal diabetic care among older age diabetics particularly those with multiple co-morbidities cannot be overemphasized. Glycaemic control was also identified as independent risk factor for development of DPN. Shaw and colleagues,[18] in their longitudinal analysis have previously demonstrated 12% higher odds for every 1mmol/l increase in fasting glucose. We used elevated HbA1c as a better indicator of chronic glycaemic control. Persistent hyperglycaemia is a strong predictor of multiple adverse outcomes among type II diabetics which may occur up to 10% higher among diabetics with HbA1c >7.0.[19] The pathways of damage resulting in DPN may be multifactorial and may involve axonal injuries, resistance to insulin, endothelial dysfunction, oxidative stresses, reduced NO, micro-vascular injury causing nerve ischemia, and the formation of advanced glycation end products. As with type 1 diabetes, guidelines suggest aggressive control in fasting and postprandial glucose for reducing the incidence and progression of DPN in any type of diabetes. Treatment regimen and central obesity were not significant hence not retained in the final model.[20] These factors have been reported previously. Possible reasons could include the use of prevalence ratios which yield better, more precise estimates compared to odds ratios. However, we did retain BMI based on its biological importance which was marginally significant. An elevated BMI is a major contributor to insulin resistance and subsequent development of DPN.[21,22]

We did not find age to be associated with DPN although reported previously.[17,23] A possible explanation could be our study sample which comprised older age patients with limited representation form younger population. Smoking status has remained inconsistent, and was not a risk factor in our study.[21,24] This could possibly be due to difficulty in classifying smokers based on participants' self-report. Alcohol use was underreported hence could not be assessed in our sample. We did not find any significant association between diabetic peripheral neuropathy and dyslipidaemia where as other people have found it.[22,25] The possible explanation for this is that, firstly, we did not do full lipid profile on all patients due to financial constraints and secondly, some of the patients might be on lipid lowering drugs that must have influenced the results of the lipid profile.

The Khyber Teaching hospital is one of the largest, public sector health facilities in the north-west region of Pakistan and serves a large catchment area representing a diverse population. Our research adds new insight into diabetic neuropathy and in a resource poor setting having a lack of high quality scientific evidence. We used a sensitive, standardized assessment for the diagnosis of DPN which is likely to result in minimal misclassification error and selection bias. The statistical analysis was based on estimation of prevalence ratios which provide more conservative estimates for analysis of cross sectional data.[26] However, we were limited to a single tertiary care facility due to financial and resource constraints, which affects generalizability of our findings. Some risk factors could not be assessed due to their low representation in our study sample. A higher sample size could possibly allow us to observe the associations with respect to these risk factors but was not feasible at this point.

Amongst the various risk factors as identified in our study, higher duration of diabetes mellitus, poor glycaemic control and raised BMI are strongly associated with DPN. Patient care should be focused on control of modifiable risk factors, however the non-modifiable risk factors should also be accounted for in the treatment plan. Greater patient care is warranted in older patients with multiple co-morbidities for improving patient outcomes in this population.

**Conflict of interest:** None declared.

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