Risk factors associated with peripheral neuropathy among diabetic individuals: a case control study

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ABSTRACT

Background: Diabetic neuropathy is one among the most common complication in diabetes mellitus. Diabetic peripheral neuropathy hinders the quality of life causing morbidity and mortality. The purpose of this study was to find the risk factors associated with diabetic neuropathy.

Methods: This case control study involved 100 diabetic patients attending the Dohnavur fellowship hospital, Dohnavur from October 2019 to March 2020. Sociodemographic profile and diabetic characteristics of the study group were obtained and analysed. Diagnosis of Diabetic Neuropathy was done by using the diagnostic method proposed by American Diabetic Association.

Results: Of the total study population with mean age 59.43 years, 63% had family history of diabetes. Almost 70% had poor diabetic control. Statistically significant relationships were found between neuropathy and duration of diabetes, glycaemic control, history of hypertension, monofilament test and pinprick sensation.

Conclusions: In this study, glycaemic control, dyslipidemia and hypertension were modifiable risk factors for diabetic neuropathy. Early interventional programs to sensitize diabetics on these factors could improve the quality of life of Diabetic patients.

Keywords: Case control study, Diabetic peripheral neuropathy, Glycaemic control, Risk factors

INTRODUCTION

Diabetes mellitus is one of the most widespread and leading cause of death in the world. There is a drastic rise in people with diabetes from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults aged 18 and above has shown a 4% rise.1 Diabetes is the leading cause of blindness, renal failure, heart attacks, stroke and lower limb amputations. Diabetic neuropathy is one of the most common chronic and debilitating complications of diabetes. Diabetic peripheral neuropathy is mainly due to persistent high blood sugar levels. Diabetic peripheral neuropathy cause is progressive, distal to proximal degeneration of peripheral nerves leading to neuropathic symptoms such as numbness, burning, prickling, tingling, sharp pains or cramps.2,3 There is a large variation in the prevalence rate of diabetic peripheral neuropathy among diabetic individuals. This variation might be due to the lack of consensus on its diagnostic criteria and variation in patient characteristics.4 Successful management of diabetes and prevention of its complication results from detection of modifiable risk factors for DPN and
preventing them at the early stages from literature review it is found that appropriate prevention can reduce ulcers by 60% and amputations by 85%.\textsuperscript{5,7}

Diabetic peripheral neuropathy results in inability to perceive the main sensations like cold, heat and pain in the extremities. Due to these lacks of sensation patient may not be aware of the presence of an ulcer in the foot. This progress into non healing ulcers and patient end up losing their limbs which in turn results in economic instability in the families. I, being a general practitioner in a fellowship hospital in rural area where people ignore the signs of nerve damage thinking that those changes happen normally due to old age, it would be of much value if I could prove scientifically that if the risk factors for diabetic peripheral neuropathy are identified at an early stage the morbidity due to the same can be minimized. The application of secondary prevention through early diagnosis and treatment is required for improving the quality of life of patients with diabetes.

This study is proposed to be conducted with the objective to find the risk factors for diabetic peripheral neuropathy and their strength of association. Thus, in the near future type 2 diabetic patients could be screened for undetected diabetic peripheral neuropathy. Aim of the study was to find the risk factors associated with diabetic peripheral neuropathy.

Objectives were to find the risk factors for diabetic peripheral neuropathy, to estimate the strength of association of each risk factors with diabetic neuropathy.

METHODS

Case-control analytical study was conducted among patients with type-2 DM attending outpatient departments of Dohnavur fellowship hospital, Dohnavur. The study was conducted from October 2019 to April 2020.

Study participants

The study included one hundred type 2 DM patients with more than 5 years duration since diagnosis and willing to participate in the study.

Cases

Diabetic patients diagnosed to have Diabetic neuropathy.

Controls

Diabetic patients without the evidence of Diabetic neuropathy.

The study participants were selected using convenient sampling. Study purpose was explained and informed verbal consent was obtained from all participants before the survey.

Exclusion criteria

Sick patients, those with other causes of neuropathy and who not giving consent for the study were excluded from the study.

Sample size

Sample size for case control study was determined using the formula described in Kelsey et al.\textsuperscript{4}

\[ n_1 = \frac{r+1}{p^2(1-p^2)} (z\beta+z\alpha/2)^2 \]

\[ n_2 = r \times n_1 \]

Where,

\[ n_1 = \text{Number of cases} \]
\[ n_2 = \text{Number of controls} \]
\[ r = \text{Ratio of controls to cases. (Taken as 1)} \]
\[ p^2 = \text{Average proportion exposed} = \text{proportion of exposed cases+proportion of controls exposed} / 2 \]
\[ p_1 = \text{Effect size or different in proportion expected based on previous studies.} \]
\[ p_2 = \text{is proportion in control.} \]
\[ Z\beta = \text{Standard normal deviate for power (power kept as 90%)} \]
\[ Z\alpha/2 = \text{Standard normal deviate for level of significance (95\% confidence interval = 1.96).} \]

Kalra et al. in the study conducted at Rajasthan in 2013 identified the proportion of cases and controls with family history of diabetes mellitus to be 33.33 and 5.35 respectively.\textsuperscript{5} Using these proportions in the above formula, the sample size was calculated to be 42 for each group which was rounded to 50 in each group.

Study tool

After enrolment of eligible subjects, A pre tested, structured questionnaire was used to collect data on demographics (age, sex, occupation), socioeconomic and lifestyle characteristics (smoking, alcohol consumption, physical activity) diabetic history (duration, treatment (insulin. Oral hypoglycaemic drugs) were collected by interviewing the participants. Biochemical parameters were derived from the latest laboratory investigation reports (in the previous 6 months) documented in the clinical records. Anthropometric measurements including weight, height, body mass index (kg/m\textsuperscript{2}) was carried out at the time of recruitment. Blood pressure was measured in the sitting position in the right arm to the nearest 2mmHg with mercury Sphygmomanometer and the participants were considered to be hypertensive if were taking antihypertensive medication or SBP≥140mmHg or DBP≥90mmHg. HbA1c was tested.

Assessment of neuropathy

The diagnostic method proposed by American Diabetes Association includes confirmed history of diabetes, presence of neuropathy during or after the diagnosis of
diabetes, presence of symptoms and signs in line with diabetic peripheral neuropathy, the evidence of clinical symptoms (pain, numbness, paraesthesia etc.) with one of the five examinations (ankle reflex, acupuncture pain, vibration sensation, temperature sensation and pressure sensation or presence of two anomalies of the five examinations despite the absence of clinical symptoms11. Neuropathy was assessed using 10-g monofilament, pinprick sensations and ankle reflexes. The monofilament was placed perpendicular to the skin and pressure applied until the filament just buckled. Based on Smieja et al, plantar sites were tested.4,10 With eyes closed, monofilament was applied (up to 3 times) for one second to the dorsum of the first toe, first, third and fifth metatarsal head. The participants indicated when the touch occurred. Inability to perceive in any one site was considered neuropathy. The monofilament (10-g) was correlated with the presence or history of ulcer and patients with risk for foot ulcer was identified.

**Statistical analysis**

The raw data was entered in to MS-excel sheet and was analysed using statistical program for social sciences (SPSS 20.0). Further statistical analysis was done using Chi-square test and adjusted Odds ratio to assess the association between diabetic neuropathy and the possible risk factors. P values were reported as specified by the statistical software used, at least up to three decimal places and those p values less than 0.05 were treated as significant.

**RESULTS**

One hundred diabetic patients were enrolled in the case control study (50 patients in each group). Out of the total study participants 76 were females. The mean age of the participants was 59.43(SD±10.615) years and the range were from 35 to 91 years. All independent variables such as sociodemographic profile, diabetic characteristics were compared with patients with or without diabetic nephropathy.

Table 1 shows the sociodemographic characteristics and their association with diabetic neuropathy. Almost half of the study participants (cases 21 and controls 24) were in the age group 50 to 59 years. Of the total respondents 78% were married. 79% of the study participants were Christian by religion. 26% of the respondents were illiterates followed by 13%,14% who have studied up to middle school, high school respectively. All the independent variables were compared with presence of absence of diabetic neuropathy. No significant association was found between diabetic neuropathy and age, gender, marital status. It is evident from Table 2 that, of the 100 respondents, 63% had family history of diabetes mellitus. Out of the 33 participants who had more than ten years duration of diabetes, 26 had developed diabetes neuropathy, duration of diabetes is also found to have statistically significant (p=0.001) association with development of diabetes neuropathy. In the current study one respondent is on insulin alone while 14 participants were on oral hypoglycemic drugs and insulin.

| Variables          | Cases | Controls | Chi square | P value |
|--------------------|-------|----------|------------|---------|
| **Gender**         |       |          |            |         |
| Male               | 14    | 10       | 0.877      | 0.349   |
| Female             | 36    | 40       |            |         |
| **Marital status** |       |          |            |         |
| Single             | 10    | 6        | 2.128      | 0.345   |
| Married            | 36    | 42       |            |         |
| Divorced/widow    | 4     | 2        |            |         |
| **Religion**       |       |          |            |         |
| Christian          | 42    | 37       | 1.507      | 0.22    |
| Hindu              | 8     | 13       |            |         |
| **Education**      |       |          |            |         |
| Post graduate      | 12    | 3        |            |         |
| Graduate           | 12    | 12       |            |         |
| Higher secondary   | 3     | 4        | 7.161      | 0.209   |
| High school        | 7     | 7        |            |         |
| Middle school      | 5     | 8        |            |         |
| Illiterate         | 11    | 16       |            |         |
| **Occupation**     |       |          |            |         |
| Professional       | 19    | 10       | 4.968      | 0.42    |
| Semi professional  | 2     | 3        |            |         |
| Skilled worker     | 5     | 6        |            |         |
| Semi-skilled worker| 3     | 7        |            |         |
| Unskilled worker   | 7     | 9        |            |         |
| Unemployed         | 14    | 15       |            |         |
Table 2: Diabetic characteristics of study participants and their association with diabetic neuropathy.

| Variable                      | Cases | Controls | Chi square | P value |
|-------------------------------|-------|----------|------------|---------|
| Family h/o diabetes           |       |          |            |         |
| Present                       | 36    | 27       | 3.475      | 0.062   |
| Absent                        | 14    | 23       |            |         |
| Duration of diabetes          |       |          |            |         |
| <10 years                     | 24    | 43       | 16.327     | 0.001** |
| >10 years                     | 26    | 7        |            |         |
| Type of treatment             |       |          |            |         |
| Oral hypoglycemic drugs       | 37    | 48       | 9.49       | 0.002** |
| Oral hypoglycemic drugs and insulin/Insulin alone | 13 | 2 | | |
| h/o hypertension              |       |          |            |         |
| Present                       | 31    | 16       | 9.033      | 0.003** |
| Absent                        | 19    | 34       |            |         |
| h/o smoking                   |       |          |            |         |
| Smoker                        | 7     | 3        | 1.778      | 0.182   |
| Non smoker                    | 43    | 47       |            |         |
| Alcohol                       |       |          |            |         |
| Drinker                       | 1     | 0        | 1.01       | 0.315   |
| Non drinker                   | 49    | 50       |            |         |
| HbB1C                         |       |          |            |         |
| <6.5 gm/dl                    | 4     | 26       | 23.048     | 0.001** |
| >6.5 gm/dl                    | 46    | 24       |            |         |
| Dyslipidemia                  |       |          |            |         |
| Absent                        | 19    | 41       | 20.167     | 0.001** |
| Present                       | 31    | 9        |            |         |
| Body mass index               |       |          |            |         |
| Underweight                   | 10    | 8        | 1.003      | 0.606   |
| Normal weight                 | 23    | 28       |            |         |
| Overweight                    | 17    | 14       |            |         |
| Blood pressure                |       |          |            |         |
| Under control                 | 20    | 41       | 18.537     | 0.001** |
| Uncontrolled                  | 30    | 9        |            |         |
| Monofilament test             |       |          |            |         |
| Normal                        | 13    | 30       | 11.917     | 0.003** |
| Reduced                       | 28    | 16       |            |         |
| Absent                        | 9     | 4        |            |         |
| Pinprick sensation            |       |          |            |         |
| Present                       | 31    | 48       | 17.42      | 0.001** |
| Absent                        | 19    | 2        |            |         |
| Ankle reflex                  |       |          |            |         |
| Present                       | 45    | 50       | 5.263      | 0.022   |
| Absent                        | 5     | 0        |            |         |

** indicates presence of statistically significant association.

Table 3: Logistic regression analysis of associated risk factors with diabetic neuropathy.

| Variable                      | Cases | Controls | P value | Adjusted OR | 95% CL |
|-------------------------------|-------|----------|---------|-------------|--------|
| Duration of diabetes          |       |          |         |             |        |
| <10 years                     | 24    | 43       | 0.013*  | 4.552       | 1.375-15.075 |
| >10 years                     | 26    | 7        |         |             |        |
| Type of treatment             |       |          |         |             |        |
| Oral hypoglycemic drugs       | 37    | 48       | 0.727   | 1.437       | 0.188-11.012 |
| Oral and insulin              | 13    | 2        |         |             |        |
| History of hypertension       |       |          |         |             |        |
| Present                       | 31    | 16       | 0.432   | 1.673       | 0.464-6.035 |
| Absent                        | 19    |          |         |             |        |
| HbA1C                         |       |          |         |             |        |
| <6.5 gm/dl                    | 4     | 26       | 0.016*  | 4.988       | 1.357-18.344 |
| >6.5 gm/dl                    | 46    | 24       |         |             |        |
| Dyslipidemia                  |       |          |         |             |        |
| Absent                        | 19    | 41       | 0.054   | 3.554       | 0.980-12.895 |
| Present                       | 31    | 9        |         |             |        |
| Blood pressure                |       |          |         |             |        |
| Under control                 | 20    | 41       | 0.076   | 3.373       | 0.880-12.931 |
| Uncontrolled                  | 30    | 9        |         |             |        |
| Monofilament test             |       |          |         |             |        |
| Normal                        | 13    | 30       | 0.128   | 1.052       | 0.162-6.821 |
| Reduced                       | 28    | 16       |         |             |        |
| Absent                        | 9     | 4        |         |             |        |
| Pinprick sensation            |       |          |         |             |        |
| Present                       | 31    | 48       | 0.015*  | 10.06       | 1.552-65.215 |
| Absent                        | 19    | 2        |         |             |        |

* indicates presence of statistically significant association.
The number of hypertensive patients with or without diabetic neuropathy were 47% and 53% respectively. Almost 70% of the study participants had poor diabetic control (HbB1C >6.5gm/dl). Type of diabetic treatment, history of hypertension, diabetic control, dyslipidemia and pinprick sensation were also found to have significant association with diabetic neuropathy with Chi square value 9.490 (p=0.002), 9.033 (p=0.003), 23.048 (p=0.001), 20.167 (p=0.001) and 17.420 (p=0.001) respectively. Whereas family history of diabetes, history of smoking, history of alcohol consumption, body mass index and ankle reflex were found to have no association with diabetic neuropathy. Table 3 illustrates the Binary logistic regression analysis performed with the factors which showed significant association with diabetic neuropathy. In regression analysis age and gender were adjusted and it was found that duration of diabetes, diabetic control (HbA1C) were statistically significant independent risk factors for diabetic neuropathy. The odds ratios were 4.552, 95% confidence interval (CI) 1.375-15.075, p<0.05 and 4.988, 95% CI: 1.357-18.344, p<0.05 respectively (given in Table 3). Those patients with more than ten years duration of diabetes had nearly 5 times more likely to develop diabetic neuropathy compared to the control group among the clinical examinations conducted (monofilament test, pinprick sensation, ankle reflex) pinprick sensation had statistically significant association (OR, 10.60, 95% CI 1. - 1.552-65.205, p=0.015). However, type of treatment (p=0.727), history of hypertension (p=0.432), dyslipidemia (p=0.054) and monofilament test (p=0.128) did not appear to be a significant predictor.

**DISCUSSION**

This study enrolled 100 diabetic patients ranging from 35-90 years of age. This study did not show any association between age and diabetic peripheral neuropathy (Chi square 9.02, p=0.108). But various other studies conducted by Christian et al., Barbosa et al., Gill et al., Zingler et al., indicated that older age group as an important determinant of diabetic peripheral neuropathy.\(^{12-15}\)

In the present study there was no association between education (Chi square 7.16, p=0.209), occupation (Chi square 4.97, p=0.42) with diabetic peripheral neuropathy. Whereas, studies conducted by Olesan et al., Gredik and Kocuglu et al., Babazadeh et al observed that patients with higher education and income had better knowledge and correct diabetes management in using oral antidiabetics and insulin.\(^{16-18}\)

In this study, smoking was not associated with DPN (p=0.182) whereas, many other studies observed significant association. Smoking increases inflammation and endothelial dysfunction thus increasing the frequency of diabetic peripheral neuropathy.\(^{19-21}\)

In the current study there was no association between obesity and diabetic peripheral neuropathy (Chi square 1.003, p=0.606). This was in contradictory the findings of studies done by Katulanda et al. (p<0.01), Mokrid et al. (p<0.01, OR 3.7, 95%CI 1.5-9.3) where they found diabetic peripheral neuropathy to be more in non-obese patients. Whereas a prospective complication study conducted by Tesfaya et al. from Europe observed diabetic peripheral neuropathy to increase with increase in body mass index (p<0.001, RR 1029, 95% CI 1.10, 1.51).\(^{22-24}\) The variations in association of diabetic peripheral neuropathy with body mass index may be due to the difference between developed and developing countries.

The current study revealed hypertension statistically significant association (Chi square 9.03, p=0.003) with DPN but failed to show as an independent predictor for diabetic peripheral neuropathy (p=0.43, OR 1.673,95% CI 0.46-6.04). This was in contrast to the study done by Pawade et al. who found hypertensive patients to have 2.95 times chance of developing diabetic peripheral neuropathy (p<0.001, OR 2.95,95% CI 1.67-5.20).\(^{25}\)

In this study though dyslipidemia had a significant association (Chi square 20.17, p=0.001) with diabetic peripheral neuropathy, the regression analysis did not show dyslipidemia as an independent predictor of diabetic peripheral neuropathy. This was again contradictory to the observations found by Pawade et al., were dyslipidemia was found to be an independent predictor (p<0.001, OR 3.18, 95% CI 1.34-7.53).\(^{21}\)

In the current study it was observed that there was a significant association between the type of diabetes treatment and diabetic peripheral neuropathy (Chi square 9.49, p=0.002). Though it wasn’t statistically proven as an independent predictor for diabetic neuropathy in the current study (p<0.73, OR 1.44, 95% CI 0.19-11.01), it was evident in many previous studies. It was shown by Mavasti al. that there was a slight increase in the odds of developing diabetic peripheral neuropathy among patients taking oral antidiabetic treatment and insulin treated group. Similarly, a cohort study conducted by Hafselejeni et al. among type 2 diabetic patients observed that in comparison to the oral treatment group, insulin treated had 1.29 odds of developing diabetic peripheral neuropathy.\(^{26}\) Curie et al in their study revealed that there was twice a chance for patients receiving insulin monotherapy and insulin plus oral hypoglycemic drugs as compared to those taking metformin alone.\(^{28}\)

In the present study it was observed that with increase in HbA1C above 6.5gm /dl there was 5 times increase in chance of developing peripheral neuropathy (p<0.01, OR 4.98, 95% CI 1.36-18.34). This was also shown by Straton et al. who in their prospective study with a follow-up period of 10 years found increase in complications by 37% for 1% increase in level of
HbA1C. Similarly, Al-Kaabi et al. found high prevalence of diabetic peripheral neuropathy among patients with poor diabetic control (OR 3.41, 95% CI 1.15-10.16) these findings were supported by the studies conducted by Morkrid et al., Edwards et al. respectively.22,30,31

CONCLUSION

The study documents that the risk factors significantly associated with diabetic neuropathy were glycaemic status, duration of diabetes, dyslipidaemia and hypertension. The results of this study could be made as a basis for future early intervention programs to prevent diabetic peripheral neuropathy and improve the quality of life for diabetic individuals.

Limitations

The study recruited only patients with Diabetic neuropathy for the case group and retrospectively reviewed the predictors of diabetic neuropathy. The possibility of recall bias is more while collecting information on diabetes characteristics of study population which may have affected the results. Another limitation of this study was the inability to accurately determine the role of traditional and cultural practices on diabetic neuropathy. To minimise the mentioned bias, a larger-scale cohort study should be conducted in the future.

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