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Evaluation of Symptomatic Peripheral Neuropathy in Type 2 Diabetes Mellitus and its Correlation with Other Microvascular Complications

Dr. Keertan Chinthamaduka[1], Dr. P. V. Makwana[2]

3rd Year Resident Doctor, Department of Medicine, Shri M.P Shah Govt. Medical College, Jamnagar, Gujarat, India
chinthamaduka.keertan[at]gmail.com

(M.D), Additional Professor, Department of General Medicine, Shri M.P Shah Govt. Medical College, Jamnagar, Gujarat, India

Abstract: ***Diabetes-related complications affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. They can be divided into vascular and non-vascular complications. The microvascular complications include retinopathy, neuropathy and nephropathy while the macrovascular complications include coronary artery disease, stroke and peripheral arterial disease. Methodology: A one-year cross sectional study was conducted in the Guru Gobind Singh Hospital, Jamnagar. 100 patient of type 2 diabetes with onset >35 years of age and patients who had symptoms of peripheral neuropathy were included in the study. Results: There is statistically significant correlation of diabetic neuropathy with other microvascular complications like diabetic retinopathy (P<0.05) and albuminuria (P<0.001). There was statistically significant correlation between diabetic peripheral neuropathy with age (p< 0.05), duration of diabetes (P<0.05), HbA1C levels (P<0.05), systemic hypertension (P<0.001) and serum triglyceride levels (p<0.05).***

Keywords: Diabetic peripheral neuropathy, Diabetic Neuropathy examination scores (DNE), Michigan Neuropathy Screening Instrument (MNSI), Microvascular complications, risk factors.

1. Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. With an increasing incidence worldwide, DM is likely to continue to be a leading cause of morbidity and mortality in the future. The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 415 million in 2017. In2019, approximately 463 million adults (20-79 years) were living with diabetes; by2045 this will rise to 700 million[8]

Diabetes-related complications affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Diabetes associated complications related to hyperglycaemia usually do not appear until the second decade of hyperglycaemia. In contrast, diabetes-associated CAD risk, related in part to insulin resistance, may develop before hyperglycaemia is established. Because type 2 DM often has a long asymptomatic period of hyperglycaemia before diagnosis, many individuals with type 2 DM have both glucose-related and insulin resistance related complications at the time of diagnosis. In view of poor awareness and lack of regular screening programmes, the initial presentation to the physicians is delayed frequently. This may predispose to increased rate of microvascular complication at onset.

The present study aims to evaluate peripheral neuropathy in type 2 diabetes patients by clinical examination correlate it with the other microvascular complications and various risk factors such as age, sex, duration of diabetes, HbA1C, body mass index and systemic hypertension. The importance of this study lies in the fact that the morbidity and mortality in diabetes is attributed to a large extent by its complications. Early detection and treatment of these complications therefore plays a crucial role. Other than glycaemic control, there are no treatments for diabetic neuropathy. Thus, identifying potentially modifiable risk factors forneuropathy is crucial. Detecting these risk factors helps in correcting these at an early stage. Correlation between the various microvascular complications helps in better understanding of their pathogenesis and early control.

2. Aims and Objectives

1) To evaluate peripheral neuropathy in symptomatic type 2 diabetes patients by clinical examination.
2) To study the correlation of diabetic peripheral neuropathy with other microvascular complications by assessing microalbuminuria and retinopathy.
3) To study the correlation of diabetic peripheral neuropathy with age, sex, duration of diabetes, body mass index and systemic hypertension.

3. Methods

This is aone-year cross sectional study conducted in the Guru Gobind Singh Hospital, Jamnagar, Gujarat. 100 patients of type 2 diabetes with onset >35 years of age and patients who had symptoms of peripheral neuropathy were included in the study. Patients with hypothyroidism, hereditary neuropathies, tuberculosis, HIV, chronic

alcoholism, patients on drugs having peripheral neuropathy as established toxicity were excluded from the study.

After prior Institutional Ethical clearance and obtaining informed consent, the participants satisfying inclusion criteria were asked detailed history and clinical examination was performed. Venous blood was drawn for fasting blood glucose levels, HbA1c levels, serum cholesterol and triglycerides. Height, weight and waist circumference of the individual patient was measured and BMI was calculated. Ophthalmological examination for diabetic retinopathy and urine analysis for albuminuria was done for all patients. Presence of peripheral neuropathy was assessed by validated Diabetic neuropathy examination (DNE) score[18] and MNSI (Michigan Neuropathy Screening Instrument) scoring system[16]. DNE score includes 4 components: muscle power, stretch reflexes, sensations of big toe and index finger. A score of > 3 indicates presence of polyneuropathy according to DNE score. MNSI has two components – a history questionnaire which is self-administered by the patient and the physical assessment scoring system. The physical assessment includes inspection of foot, vibration sensation, muscle stretch reflex and monofilament testing. A MNSI examination score of ≥2 was considered as positive for peripheral neuropathy.

Direct ophthalmoscopic examination of fundus was done and results classified as normal, mild NPDR, moderate NPDR, severe NPDR and PDR changes.Urine albumin excretion: Microalbuminuria detection was done by Albumin Creatinine Ratio estimation. Urinary albumin measured by rate Nephelometry and Urinary Creatinine measured by modified Jaffe's method. Albumin Creatinine Ratio of 30-300 g/mg of creatinine was defined as microalbuminuria; a ratio greater than 300 g/mg of creatinine was defined as macroalbuminuria. Urinary albumin detected in spot urine sample is also considered as macroalbuminuria.

Diagnosis of Diabetes based on ADA guidelines:a) Symptoms of diabetes plus random blood glucose concentration ≥200mg/dL)orb) Fasting blood sugar ≥ 126 mg/dl orc) 2hour plasma glucose≥200 mg/dl ord) HbA1c levels ≥ 6.5%

The specific risk factors studied were age, sex, duration of diabetes, HbA1C, BMI, systemic hypertension, total serum cholesterol and serum triglycerides levels.Systemic Hypertension is considered when systolic BP is ≥140 mm Hgand/or Diastolic BP ≥90 mm Hg. BMI was calculated using the formula, BMI = weight in kg/ height in m2 and values were interpreted based on the Indian standard[17]. Normal: 18-22.9 kg/m^2, overweight: 23-24.9 kg/m^2 and overweight ≥ 25kg/m^2.Total cholesterol ≥ 200 mg/dl and triglycerides ≥ 150 mg/dl were considered elevated.HbA1C is measured by bidirectionally interfaced fully automated turbidometry by Roche. Statistical analysis was done by using chi square test by Statistic calculator software version 4.8.1. A 'p value' less than 0.05 was considered significant.

4. Results

In this study, of total 100 patients, 67% of patients were males and 33%were females. 62 patients were diagnosed to have diabetic peripheral neuropathy using clinical examination scoring systems, namely DNE and MNSI scores of which 40 patients(59.8%) were male and 22(66.7%) were female patients. The mean age of diabetic peripheral neuropathy was 59.4 in male patients and was 58.6 in female patients.

31% of patients had duration of diabetes 5-10 years and only 4% had diabetes for more than 20 years. Among those patients with duration of diabetes >20 years 100% had peripheral neuropathy. The mean duration of diabetes in patients with peripheral neuropathy was found to be 10.42.

The average HbA1c of the study population was 8.83 % and that of patients with peripheral neuropathy was 9.6. 34% of the patients each had their BMI between 25-29.9 and 30-34.Out of the total 56 patients who were found to have systemic hypertension, 44 (78.6%) had peripheral neuropathy.

Hypercholesterolemia was found in 38% of patients of which 25 patients (65.8%) had peripheral neuropathy. 62% of patients had their serum cholesterol levels <200 mg/dl of which 37 patients (59.7%) also had peripheral neuropathy.55 patients(55%) were found to have triglyceride levels >150 mg/dl, of which 42 patients (76.3%) had peripheral neuropathy.

45% patients had diabetic retinopathy, of which 33 patients (73.4%) had peripheral neuropathy by clinical examination scores, while 25 (52.1%) out of 48patients those who did not have retinopathy also did not have peripheral neuropathy. 53% patients had albuminuria, of which 45(84.9%) had peripheral neuropathy by clinical examination scores, while 30(63.8%) out of 47 patients those who did not have albuminuria also did not have peripheral neuropathy.

5. Discussion

In a study done by M K Roy et al[4] in Kolkata in 2002, it was found that the nerve conduction studies were found to be abnormal only in those with clinical abnormalities as per DNE scoring. In another study which was done by Mythil et al[3] which was published in International Journal Of Diabetes In Developing Countries in 2010, it was found that out of the 71 subjects who were confirmed to have neuropathy by Nerve Conduction Studies, 59 tested positive by the DNE score which gave a sensitivity of 83%. Of the 29 subjects who were considered as not having neuropathy by the same criteria, 6 had a DNE score positive for neuropathy. The specificity of the DNE score was 79%.

Statistically significant correlation between diabetic neuropathy and retinopathy ($P<0.05$) and albuminuria ($P<0.001$) was found. Tesfaye et al[11] in the in the European Diabetes (EURODIAB) Prospective Complications Study showed evidence of a strong association between neuropathy and other microvascular complications. In the study conducted by Kumar et al[15] in Delhi it was shown that all

patients with diabetic retinopathy and 86% of patients with albuminuria were found to have peripheral neuropathy which were statistically significant.Pirart et al[6] showed positive correlation between the occurrence of diabetic neuropathy and retinopathy.

This strong correlation between various microvascular complications of diabetes further supports the fact that there is a common pathogenic mechanism underlying. Therefore, by early detection of peripheral neuropathy, urgent measures can be taken to retard the progression of other microvascular complications.

In the present study, it was found that there was statistically significant correlation between diabetic peripheral neuropathy with age ($p< 0.05$), duration of diabetes ($P<0.01$), HbA1C levels($P< 0.05$), serum triglyceride levels($p<0.05$) and systemic hypertension ($P<0.01$). It was also found that the correlation of diabetic peripheral neuropathy with sex, BMI and total serum cholesterol were not statistically significant.

Prevalence of diabetic peripheral neuropathy increases with increasing age and duration of diabetes.Similar results were found in DCCT/EDIC Study by Braffett et al[14] and in a meta-analysis study performed by Liu et al[10]

The prevalence of subjects who had HbA1c>10 was significantly higher in DPN subjects(92.3%) than in patients with no DPN (7.7%) subjects ($p<0.05$).According to a study conducted by Tesfaye et al[11], the subjects without diabetic peripheral neuropathy had good glycaemic control than in subjects with peripheral neuropathy. One of the earlier studies to establish relation between glycaemic control and neuropathy performed by Pirart[6] which showed that poor control was associated with a higher incidence of neuropathy. Holman et al, concluded that tight control of diabetes retarded or reversed the progression of the neuropathy.[7]

The prevalence of systemic hypertension in subjects with DPN (78.6%) was significantly higher than in subjects without DPN (21.4%) similar to results of Tesfaye et al[11] and Huang et al[12]

The average BMI of the study population was 27.39. The average BMI of the subjects with DPN was 27.18 and those without DPN was 27.7 ($P>0.05$). In a similar study conducted by Christine Lee et al, the average BMI of subjects with DPN was 30.7 and without DPN was 30.4 (p value >0.05).[9] Results were similar even in a meta-analysis study conducted by Liu et al[10] But Solomon Tesfaye et al, found a significant correlation between BMI and diabetic peripheral neuropathy.[5]In the study sample size is also very limited. That may account for the disparity in the observations in our study compared to Tesfaye et al.

In this study, mean total serum cholesterol was 189.58 mg/dl in subjects with DPN and 188.86 mg/dl in subjects without DPN. Mean TGL value in subjects with DPN was 157.87 mg/dl and in subjects without DPN was 137.63 mg/dl.In a similar study conducted by Katulanda et. al, the average total cholesterol level was 217.4 mg/dl in subjects with DPN and 217.1 mg/dl in subjects without DPN which was statistically insignificant. Similarly mean TGL levels in subjects with DPN was 162.1 and in subjects without DPN was 138.2 which was statistically significant($p <0.05$)[13]Total cholesterol levels did not correlate with prevalence of DPN in a meta-analysis study conducted by Liu et al[10]

6. Conclusion

Clinical examination by the DNE scores and MNSI scores is a simple, reliable and reproducible method of diagnosing diabetic peripheral neuropathy.

There is statistically significant correlation of diabetic neuropathy with other microvascular complications namely diabetic retinopathy ($P<0.05$) and albuminuria ($P<0.001$)

There was statistically significant correlation between diabetic peripheral neuropathy with age ($p< 0.05$), duration of diabetes ($P<0.01$), HbA1C levels ($P<0.05$), systemic hypertension ($P<0.01$) and serum triglyceride levels ($p<0.05$). It was also found that the correlation of diabetic peripheral neuropathy with sex, BMI, total serum cholesterol was not statistically significant.

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