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PREVALENCE OF RISK FACTORS PROMOTING DIABETIC NEUROPATHY

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ABSTRACT:

Bckground: Diabetic neuropathy is the worst consequence of diabetes mellitus leading to nerve dysfunction that is the cause of several complications such as pain, loss of sensitivity, damage to body systems, foot ulcers, morbidity and amputations etc. The aim of the present work was to study the prevalence of risk factors and occurrence of diabetic neuropathy in patients with diabetes, and how much diabetic neuropathy complications affect the life of diabetic patients.

Methods: Study in the urban areas of Karachi was conducted based on survey (interview questionnaire), and measurements/sample collection (blood pressure, physical activity, BMI, blood glucose and lipid profile) in male and female healthy controls and patients with diabetes (age range for both groups: 35-75).

Results: Results demonstrated that the family history, aging, long duration of diabetes, tobacco addiction, heavy alcohol consumption, uncontrolled glucose level, hypertension, dyslipidemia, and lack of physical activity were found to be the major factors causing increase in neuropathic complications in patients with diabetes. However, controlling the modifiable risk factors helped in improving the progression of diabetic neuropathy and general status of patients' health.

Conclusions: it is recommended that awareness should be given to diabetic patients about their life style interventions that may lead to better healthy life with fewer neuropathic complications. Conclusively, the patients could become able to successfully prevent and delay the incidence of neuropathy by proper care, healthy diet, increasing level of physical activity and controlling the risk factors.

Keywords: Diabetes mellitus, diabetic neuropathy, neuropathic risk factors, modifiable risk factors

INTRODUCTION: Diabetes mellitus is considered as a metabolic disorder wherein hyperglycemia occurs due to deficiency in production and secretion of insulin from pancreas or inability of body cells to respond to insulin secreted through pancreas, or both conditions simultaneously.[1,2] Basic and clinical research in diabetes mellitus has provided profound information on the pathophysiological constructs of diabetic complications for long term outcome research.[3] Oral and intravenous glucose tolerance tests and related other tests manifest the metabolic predictors for impaired glucose tolerance in type 2 diabetes mellitus (T2 DM) patients.[4] Diabetes may cause damage to body organs including kidneys, eyes, heart, blood vessels, nerves etc. [5] Metabolic processes are altered due to hyperglycemia resulting in oxidative stress, production of advanced glycation end products, polyol pathway influx and activation of protein kinases and hence, damage to nerves and ultimately microvascular disease and neuropathy.[6] Prevalence of T2DM increases with increase in the prevalence of obesity that necessitates to adopt weight centered approach and consider the relevance of weight in the management of T2DM patients.[7] It has been suggested that quite critical cases may require glucose range to be maintained around 140-180mg/dL by continuous infusion of insulin [1] . A recent review 8 describes the antidiabetic drugs in the management of T2DM for lowering the elevated blood level of glucose.
One of the adverse complications of diabetes is

diabetic neuropathy[9-11] that may cause multidirectional disturbances affecting different regions of body, nerve damage, disturbance in routine daily life activities and work, mood disorders, lack of sleep and energy and lack of social interaction leading to worst quality of life. Peripheral neuropathy increases the likelihood of foot complications like ulcers and amputation and Charcot joints, whereas damage to the autonomic functions including bladder problems, reproductive problems, gastric problems including nausea, appetite loss, diarrhea, constipation etc are the result of autonomic neuropathy[5] .Peripheral neuropathy is mainly responsible for morbidity and mortality in diabetic patients, and patients with sensorimotor neuropathy facing pain, numbness or tingling and loss of sensation, whereas the autonomic neuropathy may be responsible for cardiac autonomic neuropathy causing myocardial infarction, malignant arrhythmia, spontaneous death, gastro paresis, and sex related problems such as sterility, erectile dysfunction and bladder problems 6 . It has been reviewed recently. [9]

Furthermore, autonomic neuropathy increases the risk of mortality in diabetic patients through indirect mechanisms like renal failure or by direct mechanisms like cardiac failure or respiratory arrest [12] . Morphological changes in peripheral diabetic neuropathy are loss of myelination, proliferation of Schwann cells, thickening of Schwann cell basement membrane, damage and death of nerve root and axons in autonomic diabetic neuropathy sympathetic ganglia showing segmental demyelination and degeneration of axons [12] . Other changes are large sized vacuoles in sympathetic ganglion cells, swellings of dendrites and degeneration of neurons, some irregularity in esophageal nerves, reduction in density of myelinated splanchnic nerve fibers, thickening, hyperargentophilia, breaking and damaging of autonomic nerve fibers, reduction in nerve cells, greatly reduced cholinesterase activity in nerves of bladder wall, and marked reduction in number of small myelinated or unmyelinated axons in nerve biopsies in patients with diabetic peripheral or autonomic neuropathy are the important findings [12] .

The most important risk factors of diabetic neuropathy are hyperglycemia, age, duration of diabetes mellitus, visceral obesity, height, hypertension, smoking, hypoinsulinemia, and dyslipidemia [2,13] . Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes[5]. Hypertension has strong association with DSP (distal symmetric polyneuropathy) in people with short term duration or long term duration of insulin dependent diabetes mellitus (IDDM). Blood pressure is significantly higher in cases of diabetic neuropathy [14] More than 75% of adults with diabetes mellitus have blood pressure levels ≥130/80 mmHg and they use antihypertensive medication [15] .

Hypertension is considered an important risk factor for diabetic neuropathy. Hypertensives having low Na+K+ATPase activity and having polyol disturbances may lead to neurological disturbances, and those having ischemia may cause diabetic neuropathy also leading to renal disturbances [14]. Hypertension may reduce density of myelination of peripheral nerves that shows that hypertension may cause peripheral diabetic neuropathy or may exaggerate the complications of peripheral diabetes neuropathy [14].

Hyperglycemia is the main initial cause of neuropathy, retinopathy, nephropathy, and the patients are on high risk of atherosclerotic disease, heart problems, peripheral arterial disorders and cerebrovascular disease [5]. Hyperglycemia and poor glycemic control are considered as the greatest risk factors for complications associated with diabetes including nerve damage leading to diabetic neuropathy [16] though it has been suggested that recent data support the role for components in metabolic syndrome and other risk factors in the development of diabetic neuropathy that indicates the possible novel targets beyond hyperglycemia in therapeutics [10]. It has been found slightly higher in individual with IGT (impaired glucose tolerance) and IFG (impaired fasting glucose) than in individuals with NGT (normal glucose tolerance) [17]. It has been shown that high level of urinary albumin and hyperglycemia may increase the mortality risk in patients with non-insulin dependent diabetes mellitus (NIDDM) [18]. Dyslipidemia may contribute in the development of diabetic neuropathy [19]. It has been proposed that occurrence of diabetic neuropathy depends upon various risk factors including dyslipidemia, obesity, smoking and hypertension [13]. We have done several studies on the role of cholesterol in patients with diabetes mellitus [2,20-22]. Dyslipidemia may leads to cardiovascular disease that is considered as the major cause of morbidity and mortality in diabetic neuropathy[13].Obesity is the risk factor and complication in diabetes, hypertension and CVD (cardiovascular disease). About 18 million patients die per year due to CVD that relates to obesity that is considered as the risk factor for microvascular complications of diabetes such as diabetic neuropathy [23] . Defect in motor and sensory nerve conduction velocity, tactile allodynia and inability to sense alteration in temperature and impaired glucose tolerance were observed in obese mice fed with high fat diet (HFD) for inducing obesity, although when hyperglycemia was excluded the mice showed augmented sorbitol pathway activity in the

peripheral nerve, as well as 4-hydroxynonenal adduct nitrotyrosine and poly(ADP-ribose) accumulation and 12/15-lipoxygenase over expression in peripheral nerve and dorsal root ganglion neurons [24].

Cigarette-smoking associated to increased complications of diabetic neuropathy [25] might be due to any of the 4000 toxic compounds and since smoking may cause narrowing and stiffness of arteries, reducing the flow of blood in body extremities, delay in wound healing due to ischemia, insulin resistance and enhancing the risk of diabetic macrovascular and microvascular complications causing further complications in diabetic nephropathy, retinopathy and neuropathy [26]. Hence, cessation of smoking may also be effective in glycemic control [2,20,26,27].

Diabetic neuropathy including acute and chronic forms is the most common complication associated to diabetes mellitus as manifested in the research work carried out in the pathophysiological and management aspects of diabetic neuropathy over the past decade[9]. Designing the fuzzy expert system has been found quite helpful for specialists and general practitioners in detecting and diagnosing the severity of diabetic neuropathy for diagnosing the disease more quickly and improving the quality of patients' care [11]. The non modifiable risk factors of diabetic neuropathy (age, height, duration of diabetes, gender, heredity predisposition etc) have shown association with diabetic neuropathy e.g. a strong relationship between duration of diabetes, age and diabetic neuropathy; and a considerable association of gender with neuropathy; and male and tall diabetic patients of age more than 40 on risk of diabetic neuropathy[16]. Controlling the modifiable risk factors has been found to be helpful in improving the progression of diabetic neuropathy and general status of patients' health. Therefore, awareness should be given to patients about their life style interventions that may lead to better healthy life with fewer neuropathic complications in patients with diabetes mellitus.

MATERIALS AND METHODS

Research design:

This study was conducted in urban areas of Karachi. The prospective study was both survey and sample based. The sample size of study is 300 out of which 150 are control subjects and 150 are the patients. Healthy individuals were included in control group and the diabetic patients who had 5 years duration from the onset of diabetes were enrolled in patients group. The age limit for both groups ranged between 35 to 75 years of age. There was no reservation on gender of patient. The detailed questionnaire was designed by including the specific criteria. Aims and objectives of research were expressed to all study subjects. After taking the consent of subjects, the detailed questionnaire was filled out by them through interviews. Socioeconomic status, basal body weight, family history of disease, and basic inquiry about diabetes were asked from patients. Presence of risk factors of diabetic neuropathy and symptoms related to diabetic neuropathy were marked by patients. Blood pressure was recorded and estimation of glycemic and lipid levels was done. The influence of diabetic neuropathy on the quality of life of subjects in the present study was enquired from subjects and assessed.

The level of physical activity of study subjects was categorized into 3 classes- low, moderate and high. This categorization is based on PAL (physical activity level).

PAL was obtained by using the following equation:

$$PAL = \frac{TEE/24 \text{ hours}}{BMR/BEE}$$

Where,

TEE =total energy expenditure, BMR=basal metabolic rate, BEE=basal energy expenditure

Total energy expenditure (TEE) = BEE x AF

AF = activity factor

Basal energy expenditure (BEE) equation:

For males: 66+13.7(wt) +5.0(ht) -6.8(age)

For females: 655+9.6(wt) +1.8(ht)-4.7 (age)

Where, wt = basal body weight in kg, ht = body height in cm, age = age in years

PHYSICAL/PHYSIOLOGICAL MEASUREMENTS:

Blood pressure: Sphygmomanometer was used to measure the blood pressure. Before taking recordings of BP the study subject was asked to relax and sit back calmly with ease. After 5 minutes the deflated cuff was wrapped around the bare upper arm and the valve on the rubber bulb was closed. The stethoscope was placed over the pulse, under the cuff. The cuff was then pumped up by squeezing the bulb, and as the pressure was released the korotkoff sounds were heard through the ear pieces of the stethoscope. The blood pressure (systolic/diastolic) was measured in terms of millimeters of mercury mm Hg.

BMI: In order to determine whether the patient was obese or not, the body mass index (BMI) was calculated for every individual in the study. After measuring the basal body weight in kilograms and height in meters, BMI was calculated by using Metric formula.

Diagnostic tests:

Blood glucose level: Blood glucose level of study subjects was checked by using glucometer. First enquired from the patients whether they were in fasting state or random state, and instructed for fasting level requirements with their consent. A new lancet and strip was utilized for each subject. A cotton swab dipped in alcohol was taken for cleaning the index finger of study subjects before pricking. Subjects were instructed to place the drop of blood on the strip on the place of mark, and then to wait till reading appears on the screen. Readings were noted and recorded.

Lipid profile:

The lipid profile (levels of LDL, HDL and VLDL) was done by kit method. Blood of patients was taken and centrifuged. Plasma was stored in refrigerator at required temperature. Later the aliquots of the sample were used for the assessment of lipid profile.

Statistical analysis:

Statistical analysis and comparisons were carried out by assessing the range, percentage and mean values. Chi-square test was applied to check the significance levels of the relevant data. The p value <0.05 was considered significant, p value<0.01 highly significant and p value<0.001 very highly significant.

RESULTS AND DISCUSSION

Results obtained in the present study (n: 300; 50 % healthy control subjects and 50% diabetic patients) were obtained from two groups, the control group (38.67 % male subjects, 61.33 % female subjects) and the patients group (45.33% males, 54.67 females) (Figure 1).

Fig 1

Influence of age in the present study was analyzed for the subjects in the range of 35 to 75 years age. The range of age group was further divided into four groups mentioned below.
It is shown in Figure 2 that the range values of age in four age groups were:
Age group I: (36-45 years; 16.67% patients of total patients, 47.33% controls of total controls)
Age group II: (46-55 years; 42.67% patients of total patients, 23.33% controls of total controls)
Age group III:(56-65 years; 28.67% patients of total patients, 19.33% controls of total controls)
Age group IV:(66-75 years; 12.00% patients of total patients, 10.00% controls of total controls)

Fig 2

Figure 3 shows that diabetes and other complications associated to diabetic neuropathy had strong relation with inheritance. The patients had higher family history of disease. 82.67% of patients and 32.67 % of controls had family history of diabetes. 60.67% patents and 25.33% controls reported family history of hypertension. Family history of kidney diseases was reported by 26% of patients and 6% of controls. It was found that 48% patients and 4.67% of controls had family history of CVD.

Fig 3

Figure 4 shows that the study subjects had a variety of chronic diseases. Zero % patients and 0% controls had diabetes type 1. Diabetes type 2 was reported by 100% of patients and 0% of controls, 62% patients and 0.67% of controls had dyslipidemia. Hypertension was observed in 72% of patients and 0% of controls. The prevalence of CVD was 0% in controls and 10% in patients. The lung disorders were 2.67% in patients and 0% in controls. Zero % of controls and 5.33% of patients specifically had kidney disorders.

Fig 4

It was observed that the level of physical activity was poor in patients as compared to controls. 66.67% patients and 38% of controls had low level of physical activity. 27.33% patients and 42.67% controls had moderate level of physical activity. High level of physical activity was observed in 19.33% of controls and only 6% of patients (Figure 5).

Fig 5

The unawareness and carelessness were observed high in population. Majority of patients were unaware of the importance of checking blood sugar level. 24.67% patients reported that they check their blood sugar once a week. Twice in a week was reported by 8.67% patients. 6.67% patients told that they check their sugar level thrice a week. 3.33% patients reported that they check their sugar level 4 to 5 times a week. 2.67% were those checking six times a week. 8.67 % majority of those who were on insulin reported that they check their blood sugar level daily. 42% patients are those who reported that they do not check their blood sugar in a week (Figure 6).

Fig 6

Figure 7 shows that the prevalence of all risk factors such as tobacco addiction, heavy alcohol consumption, hypertension, hyperglycemia, obesity, kidney disorders was significantly higher ($p<0.05$) in patients group as

compare to controls group. The prevalence of tobacco addiction was observed 0% in control and 32% in patients group. Alcohol addiction was obtained in very few percent of population because of religious terms and conditions but in patient group 3.33 % of alcohol addiction was observed while in control it was observed in 0% of study subjects. The prevalence of renal disease was observed 0% in control group and 10% in patient group. Hyperglycemia was found markedly higher in patient group which was 80% whereas in control group its prevalence was 0%. Hypertension was the 2nd highest risk factor which was observed to be 76.67% in patient group and 0% in controls. Dyslipidemia was found in higher percentage in patient group about 60% and 0% in control group. Obesity was observed 60% in patient group which is quite high than in control group which had 3.33% prevalence of obesity.

Fig 7

Table 1 shows the prevalence of symptoms in study subjects. It was observed that the prevalence of the observed symptoms were significantly higher ($p<0.05$) in patient group as compared to control group.

TABLE 1

Figure 8 shows the level of severity of diabetic neuropathy in patient group. 13.33% of patients were reported little severe level of diabetic neuropathy, 30.67% were reported moderate level of severity in diabetic neuropathy and 56% of patients were claimed high level of severity.

Fig 8

Diabetic neuropathy was observed to become worsen with time so large number of patients claimed that the complications and symptoms related to diabetic neuropathy were going to exaggerate with time (Figure 9).

Fig 9

The 20% subjects reported that diabetic neuropathy put little impact on their life, 32% reported that diabetic neuropathy added moderate level of complications on their life and 48% reported that diabetic neuropathy harshly put high level of bad impact on their life (Figure 10).

Fig 10

In the present study, it was observed that diabetic neuropathy has direct relationship with duration of diabetes since 94% patients showed long duration of diabetes at least for more than 5 years. Detailed studies about the insights for the diagnostic and management aspects 9-11 are helpful in interpreting the findings. In accordance to present study smoking and alcohol addiction, hypertension, hyperglycemia, kidney disease, dyslipidemia and obesity are the important risk factors of diabetic neuropathy. It was revealed 12 that the significant correlation was present between prevalence of diabetic neuropathy with smoking ($p<0.001$), dyslipidemia ($p<0.001$). The significant correlation existed between prevalence of symptoms of diabetic neuropathy in patient who had tobacco addiction. The prevalence of tobacco addiction is significantly higher in patients in comparison of control ($p<0.05$). In present study the prevalence of smoking is 32% patients and 0% in controls. The prevalence of dyslipidemia was extensively studied in one study in patients with diabetic neuropathy 28 . In present study the dyslipidemia is significantly higher in patients ($p<0.05$) than control group. Dyslipidemia was observed 0.67% in controls and 60% in patients. It has been concluded that the hyperglycemia is responsible for neural and vascular damage. In another study, 38% diabetic patients showed hyperglycemia 29 . In present study 80% patients had hyperglycemia. The prevalence of hyperglycemia is significantly higher in patients than control ($p<0.05$), therefore according to present study the hyperglycemia is the major risk factor for complications of diabetic neuropathy. It was found 14 that long duration of diabetes, uncontrolled blood pressure, hypertension, hyperglycemia and smoking were all independent risk factors of the likelihood of distal symmetric polyneuropathy (all $p < 0.0001$, except for smoking for which $p = 0.03$). The hypertension was noted to have relationship with vascular disease in diabetes [30] . The blood pressure was higher in patients than control group. Similar results for the role of blood pressure in patients with diabetes mellitus were obtained in another study[2] . In our current study, it is also evident that hypertension that was 76.67% in patient group and 0% in control group ; and there was significant ($p<0.05$) relationship between hypertension and diabetic neuropathy. Electrolyte changes in patients with diabetes mellitus obtained in our previous work 2,21 is quite interesting and provides evidence of the influence of blood pressure in diabetes mellitus. Neuropathy may occur in at least 65% of patients who are about to begin dialysis for chronic renal failure 31 . In the present study the prevalence of kidney disease is significantly higher ($p<0.05$) in patients as compared to control group. Prevalence of neuropathy in patients with renal disease was evaluated that provided better idea [32] . Alcohol consumption may be responsible for absence of leg reflexes and autonomic dysfunction but there was no

significant correlation between of alcohol consumption and neuropathy [13] . In our study the prevalence of alcohol consumption was 3.33% in patient group and 0% in control group. It was found that the obese patients showed significantly decreased compound muscle action potential amplitude of tibial and peroneal nerves and decreased sensory action potential amplitude of all nerves[33] . Most of the sensory thresholds were altered in obese patients. Insulin serum levels were significantly increased in obese patients. It was also observed that high level of triglycerides and BMI higher than 30 were risk factors for progression of complication related to diabetic neuropathy [34] . These factors enhanced the risk of neuropathy ($p<0.05$). It was observed that obesity and triglycerides were related to loss of small unmyelinated axons. These findings indicated that obesity and hyperglycemia significantly increase risk for peripheral neuropathy, independent of glucose control. In our study it was observed that the prevalence of obesity was significantly higher in patient with diabetic neuropathy than to control group ($p>0.05$).The prevalence of obesity is 60% in patient group and 3.33% in control group. The exercise intervention had been associated with improved neuropathic symptoms, nerve function, and cutaneous innervation in patients with peripheral diabetic neuropathy [35] . They observed the significant reduction in pain (− 18.1 ± 35.5 mm on a 100 mm scale, $p = .05$), neuropathic symptoms (− 1.24 ± 1.8 on mnsi, $p = .01$), and increased intra epidermal nerve fiber branching (+ 0.11 ± 0.15 branch nodes/fiber, $p = .008$) in patients who did aerobics and other strenuous exercise. There was positive association between physical activity and health-related quality of life 36 . In present study, there was highly significant low level of physical activity observed in patient group in comparison with control group ($p>0.0001$). Our previous studies also point out the involvement of physical activity and diet in diabetes mellitus 2,21 .It was investigated that diabetic neuropathy put significant impact on the quality of life and diabetic neuropathy was considered as financial burden 37 . In our study the higher number of patients complained for symptoms of peripheral neuropathy such as muscle weakness especially in legs 88%, bone and joint pain 79%, numbness and tingling 76% and sharp pain and cramps 72% (Table 1). The quality of life (QOL) was found to be badly affected by diabetic neuropathy 38 that was assessed by the QOL using the Nottingham health profile (NHP). The NHP was based on six domains assessing energy, sleep, pain, physical mobility, emotional reactions and social isolation. The diabetic patients who had neuropathic symptoms had significantly higher scores (impaired QOL) in 5/6 in that assessment of NHP domains than the diabetic patients who had no symptoms of neuropathy ($p < 0.01$) or than who were non-diabetic ($p < 0.001$) controls. The diabetic patients with neuropathy had emotional distress, lack of energy, pain, physical mobility and sleep disturbance. In the current study little impact of neuropathy was reported by 13.33% of patients, moderate impact of neuropathy was observed in 30.67% of patients while high impact of neuropathy on quality of life was reported as 56% of patients. Our previous work on endothelial dysfunction, cytokines and diabetes mellitus 2,22,27,39 specially leptin 2,20,21,39 and ischemia and adipokines 2,20 emphasizes for studying the involvement of cytokines and ischemia in relation to various risk factors in patients with diabetes mellitus and diabetic patients with diabetic neuropathy. Hence, to clarify the pathobiological aspects in diabetic neuropathy requires further studies considering the important and recent investigations 1-4,7-11,40 to understand the pathophysiological changes occurring in diabetic/ diabetic neuropathic patients with various risk factors.

CONCLUSIONS

The prevalence of diabetic mellitus type 2 has increased much in our population and complications associated with diabetes are also increasing day by day. One of the major complications of diabetes is diabetic neuropathy. The prevalence of diabetic neuropathy is quite high in our population and it is is increasing gradually because of unawareness of risk factors that contribute in adding complications in diabetic patients. Therefore, the patients could become able to successfully prevent and delay the incidence of neuropathy by proper care, healthy diet, increasing level of physical activity and controlling the risk factors.

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Aisha Qadir; data collection, data analysis, manuscript writing, manuscript review
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Ghazala Yasmeen; manuscript writing, manuscript review