

PREVALENCE OF RISK FACTORS PROMOTING DIABETIC NEUROPATHY

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ABSTRACT

Diabetic neuropathy is the worst consequence of diabetes mellitus leading to nerve dysfunction and it 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 that may promote diabetic neuropathy in patients with diabetes mellitus type-2. A study 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 patients with diabetes. Age range of the subjects was 35-75 years. The results showed significant variations for hypertension, obesity, dyslipidemia, smoking and kidney disorders (compared between the male and female patients) that may promote neuropathic complications in patients with diabetes. However, controlling the important modifiable risk factors is helpful in improving the progression of diabetic neuropathy and general status of patients' health. Hence, it is recommended that awareness should be given to diabetic patients about their life style interventions especially via decreasing the risk factors that may lead to better healthy life with fewer neuropathic complications.

KEYWORDS: Diabetes mellitus, Diabetic neuropathy, Risk factors, Hypertension, Obesity, Dyslipidemia, Smoking, Kidney problems.

INTRODUCTION

Diabetes mellitus is considered as a metabolic disorder wherein chronic increase in blood glucose occurs over a prolonged period due to deficiency in production of enough insulin from pancreas or inability of body cells to respond to insulin secreted through the pancreas, or both conditions occurring simultaneously (Alam *et al.*, 2014; Sohail, 2015; Cheisson *et al.*, 2018). Major types of diabetes are insulin-dependent-diabetes mellitus (IDDM) or Type-I (TI-DM), noninsulin-dependent-diabetes (NIDDM) or type-2 (T2-DM) and gestational diabetes.

Clinical and basic research in diabetes mellitus has provided enormous information on the diagnostic, pathophysiological and management aspects of diabetic disorders for long term outcome research studies (Schwartz *et al.*, 2017; Cheisson *et al.*, 2018). Fasting glucose levels, oral and intravenous glucose tolerance tests, glycated hemoglobin and related other tests provide information for metabolic diagnostic predictors for assessing impaired glucose tolerance in type-2 diabetes mellitus patients (Henninger *et al.*, 2015; Park *et al.*, 2018).

Diabetes may cause damage to body organs (Mellitus, 2005), and oxidative stress (Robson *et al.*, 2017), production of the advanced glycation end products (Robson *et al.*, 2017), influx of polyol pathway (Lu *et al.*, 2018), obesity (Nimitphong *et al.*, 2018), activation of protein kinases (Madhavi *et al.*, 2018) and damage of nerves (Gonçalves *et al.*, 2017; Madhavi *et al.*, 2018) that may lead to neuropathy (Gorgojo Martínez, 2016; Madhavi *et al.*, 2018). The range of approximately 140-180mg/dL for glucose levels might be required to be maintained even in quite critical cases (Alam *et al.*, 2014). We have done several studies on the role of cholesterol in patients with diabetes mellitus (Hussain *et al.*, 2007b; Sohail and Hussain, 2008; Sohail *et al.*, 2013; Sohail, 2015) showing the role of dyslipidemia in diabetes. A recent review (Chaudhury *et al.*, 2017) describes the antidiabetic drugs in the management of T2DM for lowering the elevated blood level of glucose.

Diabetic neuropathy causes a variety of disturbances (Mellitus, 2005; Juster-Switlyk and Smith, 2016; Grisold *et al.*, 2017; Rahmani Katigari *et al.*, 2017). It manifests a variety of changes and has been reviewed recently (Juster-Switlyk and Smith, 2016).

It has been revealed that hyperglycemia/poor glycemic control are the risk factors greatly related with the disorders of diabetes causing diabetic neuropathy (Madhavi *et al.*, 2018). The important risk factors in diabetic neuropathy are hyperglycemia, age, obesity (especially visceral), hypoinsulinemia, duration of diabetes mellitus, BMI, smoking (Hussain *et al.*, 2007a; Sohail *et al.*, 2013; Sohail, 2015), hypertension, dyslipidemia etc (Tesfaye *et al.*, 1996; Mellitus, 2005; Hussain *et al.*, 2007a; Sohail and Hussain, 2008; Sohail *et al.*, 2013; Sohail, 2015; Ohishi, 2018). Dyslipidemia may cause cardiovascular disorder - the main cause of morbidity/ mortality in diabetic neuropathy (Tesfaye *et al.*, 1996). Several variables e.g. age, height, gender, inheritance, duration of disease and other non modifiable risk factors associate with diabetic neuropathy. On the other hand control of modifiable risk factors is quite helpful in the general health status and improvement in the diabetic neuropathy condition.

It seems necessary for the patients with diabetic neuropathy to have awareness about their lifestyle that might lead to decrease in neuropathic conditions. 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. In view of that, we planned the present study to have better and more detailed information of the prevalence of risk factors promoting diabetic neuropathy.

MATERIALS AND METHODS

This study was conducted in urban areas of Karachi. The prospective study was both survey and sample based. The sample size in the study constituted 1500 subjects with diabetes mellitus (male: 1000; female: 500). The diabetic patients who had about 5 year onset of diabetes were enrolled in the present study. The age limit ranged between 35 to 75 years.

The detailed questionnaire was designed by including the specific criteria. Aims and objectives of research were explained to all study subjects. After taking the consent of subjects, the detailed questionnaire was filled out by them through interviews. The percentage data in the present study was compared between male and female diabetic patients. The Student t test and Z scores were applied where required. The p value <0.05 was considered statistically significant.

Socioeconomic status, basal body weight, family history of disease, and basic inquiry about diabetes were asked from patients. Presence of risk factors symptoms/ disorders in patients with diabetes were recorded and compared between men and women. Blood pressure was recorded and estimation of glycemic and lipid levels was done. The influence of risk factors that may promote diabetic neuropathy and their influence on the quality of life of subjects in the present study were 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) that was calculated by dividing the total energy expenditure (TEE) in 24 hours by BMR per basal energy expenditure (BEE). Whereas BEE standard values for men and women are considered as $66+13.7(\text{wt})+5.0(\text{ht})-6.8(\text{age})$ and $655+9.6(\text{wt})+1.8(\text{ht})-4.7(\text{age})$, respectively.

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.

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.

The lipid profile (blood levels of LDL and HDL) 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.

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 used by 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.

RESULTS

Figure 1 shows the risk factors in patients with diabetes mellitus that may promote diabetes neuropathy. The prevalence of obesity in these patients (male: 60.5% (n: 605); female: 68.8% (n:344) showed significant difference (Z score: -3.1434; p-value: 0.00168), and the second highest in female patients (Fig. 1). Hypertension was found highest in both male and female patients (male: 76.6% (n:766); female: 70.0% (n:350) (Fig. 1) and its variation between the male and female patients was found significant (Z score: 2.7611; p-value: 0.00578).

Dyslipidemia was the second highest in male patients and the third highest in female patients (Fig. 1). Its prevalence in male and female patients respectively was as 62% (n:620) and 56.2% (n:281) showing significant variation (Z score: 2.1621; p-value: 0.03078). Tobacco-addiction was the fourth highest risk factor in male and fifth in female patients (Fig. 1; male: 42.2% (n:422); 5.8% (n:29) indicating significant difference (Z score: 14.4929; p-value: <0.001). However, Kidney-disorders were the 4th highest risk factor in female patients (13.4% (n:67) and 5th in male patients (12.3% (n:123) showing no significant variation (Fig. 1) between male and female patients (Z score: -0.6038; p-value: 0.5485).

Table 1 shows the prevalence of symptoms in male and female patients with diabetes mellitus that may promote diabetic neuropathy.

Prevalence of symptoms/ disorders having high prevalence were light to dark eye adjusting-problems, problem of eyes, and sharp pain (or cramps) in male patients and bone& joint pain, muscle weakness (especially in legs), and cardiovascular-complications in female subjects (Table 1). Significant variation was found for hypoglycemic-unawareness, muscle weakness (especially in legs), cardiovascular-complications, bone& joint pain, respiratory-arrest, breath-shortness, numbness (or tingling), infections and loss of balance & coordination (p<0.05). All other recorded symptoms/ disorders (Table 1) did not show any significant variations.

It was observed that the level of physical activity was poor in the patients with diabetes. The 66.67% patients had low level of physical activity; 27.33% patients showed moderate level of physical activity; and only 6% of patients had high level of physical activity (p<0.05). The 20% subjects reported that diabetes 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 ($p < 0.05$).

The unawareness and carelessness were observed high in several groups of diabetic patients. Majority of patients were unaware of the importance of checking blood sugar level. The 24.6% patients reported that they check their blood glucose once a week; 9.7% patients reported that they check twice in a week. 8.7% patients told that they check thrice a week; 3.5% patients reported that they check 4 to 5 times a week; 2.8% were those checking six times a week; 8.7% of those reported that they check their blood glucose level daily. The 42% reported that they check their blood glucose not weekly. A significant variation among several groups of patients was noted ($p < 0.05$).

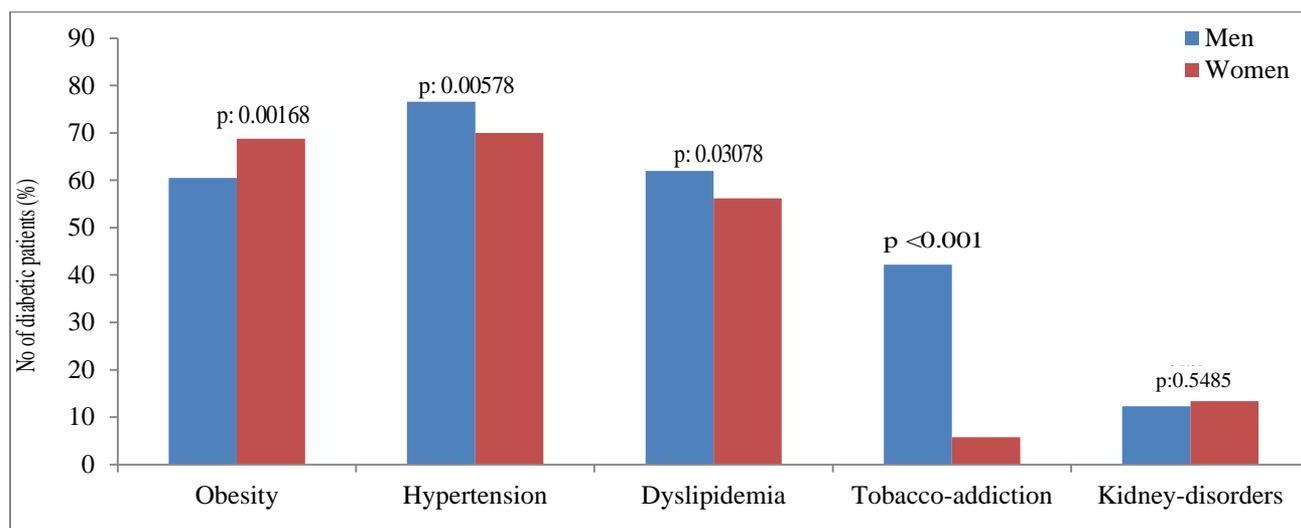


Fig. 1. Prevalence of risk factors that may promote diabetic neuropathy.

Table 1. Prevalence of symptoms in male and female patients with diabetes mellitus that may promote diabetic neuropathy.

Symptoms in patients with diabetes mellitus (n: 1500)	Prevalence				Z score	p-value
	Men		Women			
	n ^{*1}	%	n ^{*2}	%		
Hypoglycemic-unawareness	395	39.50	226	45.20	-2.1128	<0.03
Sharp pain(or cramps)	724	72.40	364	72.80	-0.1636	<0.87
Muscle weakness(especially in legs)	680	68.00	420	84.00	-6.6058	<0.01
Cardiovascular-complications	593	59.30	396	79.20	-7.6661	<0.01
Loss of HRV	400	40.00	203	40.60	-0.2234	<0.83
Increase in heart-rate while in rest	554	55.40	268	53.60	0.6603	<0.51
Incontinence-occurrence	317	31.70	171	34.20	-0.9743	<0.33
Bone& joint pain	699	69.90	434	86.80	-7.1774	<0.01
Light to dark eye adjusting-problems	801	80.10	390	78.00	0.948	<0.34
Increased-sweating	666	66.60	316	63.20	1.3055	<0.19
Decreased-sweating	235	23.50	124	24.80	-0.5563	<0.58
Change in touch-sensitivity	633	63.30	329	65.80	-0.9517	<0.34
Respiratory-arrest	502	50.20	322	64.40	-5.2105	<0.01
Breath-shortness	528	52.80	297	59.40	-2.4221	<0.02
Nausea-occurrence	353	35.30	190	38.00	-1.0257	<0.30
Bloating-occurrence	406	40.60	226	45.20	-1.7009	<0.09
Constipation-occurrence	540	54.00	245	49.00	1.8277	<0.07
Diarrhea-occurrence	253	25.30	110	22.00	1.4067	<0.16
Problem for bladder-emptying	381	38.10	205	41.00	-1.0852	<0.28
Deformities	346	34.60	177	35.40	-0.3065	<0.76
Appetite-loss	341	34.10	190	38.00	-1.489	<0.14
Problem of eyes	726	72.60	376	75.20	-1.0752	<0.28
Postural-hypotension	477	47.70	244	48.80	-0.402	<0.69
Numbness(or tingling)	561	56.10	252	50.40	1.7233	<0.04
Infections	430	43.00	270	54.00	-4.0256	<0.01
Loss of balance& coordination	623	62.30	365	73.00	-4.12	<0.01

n: number of subjects; ^{*1} number of male subjects: 1000; ^{*2} number of female subjects: 500

DISCUSSION

Detailed studies about the insights for the clinical, diagnostic and management aspects (Juster-Switlyk and Smith, 2016; Grisold *et al.*, 2017; Rahmani Katigari *et al.*, 2017; Nimitphong *et al.*, 2018) are helpful in interpreting the findings in the present study that hypertension, obesity, dyslipidemia, smoking, and kidney disease are the important risk factors that may promote diabetic neuropathy.

It was revealed (Tefsaye *et al.*, 1996) that the significant correlation was present between prevalence of diabetic neuropathy with dyslipidemia ($p < 0.001$) and smoking ($p < 0.001$). This study (Tefsaye *et al.*, 1996) that is quite similar to our current work specifically suggested that significant correlation was found between prevalence of symptoms of diabetic neuropathy in patient who had tobacco addiction. However, though smoking is one prominent risk factor in our current study, the risk factors with highest occurrence in higher to lower order in our present study were hypertension, dyslipidemia, obesity, smoking and kidney problems for male patients; and hypertension, obesity, dyslipidemia, kidney problems and smoking in female patients with diabetes mellitus.

Prevalence of dyslipidemia is one of the major risk factor in diabetic male and female patients in our present work, that is similar to a study wherein the prevalence of dyslipidemia was extensively studied in patients with diabetic neuropathy (Vincent *et al.*, 2009). Similar to our study indicating hypertension as the highest risk factor, hypertension was noted to have relationship with vascular disease in diabetes (Estacio *et al.*, 2000; Ohishi, 2018). Similar results for the role of blood pressure in patients with diabetes mellitus were obtained in our previous study (Sohail, 2015). Electrolyte changes obtained in patients with diabetes mellitus in our previous work (Sohail and Hussain, 2008; Sohail, 2015) are quite interesting and provide evidence of the influence of blood pressure in diabetes mellitus.

The investigation that neuropathy may occur in at least 65% of patients who are about to begin dialysis for chronic renal failure (Raskin *et al.*, 1976; Baumgaertel *et al.*, 2014) provides evidence to interpret our present study wherein the prevalence of kidney disease is significantly involved in patients with diabetes. Obesity was found related to causing diabetic neuropathy in patients with diabetes mellitus (Miscio *et al.*, 2005; Smith and Singleton, 2013; Nimitphong *et al.*, 2018) that provides evidence for the high occurrence of obesity as a risk factor in our present study.

Our previous work on endothelial dysfunction, cytokines and diabetes mellitus (Hussain *et al.*, 2007a; Hussain *et al.*, 2007b; Sohail and Hussain, 2013; Sohail, 2015), specially leptin (Sohail and Hussain, 2008; Sohail *et al.*, 2013; Sohail and Hussain, 2013; Sohail, 2015) and ischemia and adipokines (Sohail and Hussain, 2013; Sohail, 2015) 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 investigations (Sohail and Hussain, 2009; Alam *et al.*, 2014; De Visser *et al.*, 2014; Henninger *et al.*, 2015; Sohail, 2015; Gorgojo Martínez, 2016; Juster-Switlyk and Smith, 2016; Chaudhury *et al.*, 2017; Grisold *et al.*, 2017; Rahmani Katigari *et al.*, 2017; Schwartz *et al.*, 2017) to understand the pathophysiological changes occurring in diabetes/ 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 increasing gradually because of unawareness of risk factors that contribute in adding complications in diabetic patients. Therefore, the patients with diabetes could 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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(Received April 2017; Accepted June 2017)