FREQUENCY OF CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objectives: To determine the frequency of cardiac autonomic neuropathy in patients with type 2 diabetes mellitus.

Study Design: Descriptive (Cross Sectional) Study

Study Settings: Medical-A unit, Department of Medicine, Hayatabad Medical Complex Peshawar.

Study Duration: The duration of this study was one year, carried out from January, 2011 to December, 2011.

Subjects and Methods: The study was conducted after approval from hospitals ethical and research committee. The patients included in the study through OPD and admitted to the Medical Department of the hospital for further evaluation. All patients meeting the inclusion criteria with fasting blood glucose of > 126mg/dl with history of intake of hypoglycemic drugs and a duration of minimum 10 years were included in the study. The purpose and benefits of the study were explained to the patients and a written informed consent was obtained.

Result: A total of 127 patients of type 2 diabetes mellitus with mean age of 53.08 ±7.8 years, ranged from 35 to 68 years were enrolled in this study. Gender distribution of total patients showed that 71(56%) patients were male while 56(44%) patients were female. Among them 41.4% were male and 43.9% were female diabetic patients suffering from CAN. The mean duration of diabetes mellitus was 13.83 ± 3.48 years with minimum duration of 10 years and maximum duration of 25 years. The frequency of CAN in these patients of type 2 diabetes mellitus was 42.5%. The highest frequency 76.9% of CAN was found among patients with duration of diabetes for >20 years.

Conclusion: Cardiac autonomic neuropathy is very common in type 2 diabetes mellitus. It results in increased morbidity and mortality. Thus every type 2 diabetic patient should be screened for cardiac automatic neuropathy.

Key Words: Diabetes, cardiac autonomic neuropathy.

INTRODUCTION

Diabetes mellitus (DM) has become a major health problem worldwide. In Pakistan, the prevalence of diabetes mellitus is reported as high as 10% among adults[1]. There are two predominant forms of diabetes mellitus, which are type 1 and type 2 DM. Type 2 DM is the more common form of the two. This disease if not properly controlled can lead to a number of serious complications. The most important of these complications include Neuropathy, Retinopathy, Nephropathy, Ischemic heart disease, Stroke and Diabetic foot[2].

Among neuropathic complications, Autonomic neuropathy is an important complication of diabetes mellitus. It results from damage to autonomic nerve fibers. The potential mechanisms of this damage include metabolic insult, neurovascular insufficiency, autoimmune damage and activation of the polyol pathway leading to accumulation of sorbitol[3]. Diabetic autonomic neuropathy can affect different organ systems including gastrointestinal tract, urogenital tract and cardiovascular system[4].

Cardiac autonomic neuropathy (CAN) is the most serious complication among diabetic autonomic neuropathies. Cardiac autonomic neuropathy may be present at the time of diagnosis of DM, however its prevalence increases with age, duration of diabetes, and poor glycemic control[5]. Due to these factors the prevalence of cardiac autonomic neuropathy varies widely among diabetic patients. However the prevalence in patients with long standing DM i.e. of more than 10 years duration varies from 51% to 86%. In Pakistan the prevalence of cardiac autonomic neuropathy in long standing type 2 DM is 30%[6]. Cardiac autonomic neuropathy in diabetic patients is associated with significantly increased morbidity and mortality[4]. This is mainly because of increased incidence of cardiac arrhythmias, silent myocardial ischemia and sudden cardiac death[7].

Many patients with long standing type 2 DM have sub clinical cardiac autonomic neuropathy. The earliest clinical sign of cardiac autonomic neuropathy is reduced heart rate variability (HRV). Later on the patient develops resting tachycardia, exercise intolerance and orthostatic hypotension. There is increasing re-

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duction in HRV as cardiac autonomic neuropathy progresses with time[4]. Thus tests of HRV are considered as standard screening tests for the diagnosis of CAN[5].

The three standard tests include the Expiration to inspiration (E/I) ratio, heart rate response to posture change and to Valsalva maneuver[8]. Because of serious consequences of cardiac autonomic neuropathy in diabetes it is important to prevent its development as well as delay its progression if it has developed. This can be done through tight control of hyperglycemia, hypertension, hyperlipidemia and treatment of microalbuminuria[9]. Patients with diabetic cardiac autonomic neuropathy along with above measures should also be started on regular Angiotensin-converting enzyme inhibitors and beta-Blockers[10].

As cardiac autonomic neuropathy is a very serious complication of diabetes mellitus and is responsible for most of the atypical symptoms like silent myocardial infarction, and very few studies have been done in Pakistan to find its prevalence in type 2 DM, I therefore decided to conduct this study to find out the frequency of cardiac autonomic neuropathy in patients with type 2 diabetes mellitus in our local population. The results of this study will help in creating awareness among the physicians towards this important and serious but preventable complication of diabetes and if found in significant number of patients with DM we will recommend the regular screening of patients with long standing DM which will help us to diagnose it at its earliest stage and hinder its progression through strict glycemic control and use of beta blockers and Angiotensin converting enzyme inhibitors.

OBJECTIVE

To determine the frequency of cardiac autonomic neuropathy in patients with type 2 diabetes mellitus.

MATERIAL AND METHODS

This Observational Study was performed in Medical-A Unit, Department of Medicine, Hayatabad Medical Complex, Peshawar from January 2011 to December 2011. A total of 127 patients were enrolled in this study as per inclusions criteria mentioned below.

SAMPLE SELECTION

Inclusion Criteria

1. All Patients with Type 2 Diabetes mellitus of more than 10 years duration
2. Between 35 —75 years of age and of both sexes

Exclusion Criteria

1. Mentally ill patients or patients unable to undertake the test.
2. Patients with any severe additional medical disorder like Liver cirrhosis (past medical records), heart failure (on Echocardiography), severe infection (through history and clinical examination) or chronic renal failure (serum creatinine>1.1).
3. Patients with Atrial fibrillation diagnosed on ECG.
4. Patients receiving beta blockers and calcium channel blocker drugs as detected by history.

OPERATIONAL DEFINITION

Type 2 Diabetes Mellitus: Patients with Fasting blood glucose of > 126mg/dl measured in the laboratory with history of intake of hypoglycemic drugs were labeled type 2 Diabetes Mellitus.

Cardiac Autonomic Neuropathy: It was diagnosed on the basis of presence of any one of the following feature on Electrocardiographic examination:

1. Abnormal Expiration Inspiration (E/I) Ratio.
2. Abnormal Heart Rate Response to Postural Change of < 1.03.
3. Abnormal Valsalva Ratio < 1.2.

Dignosticcriteria for Cardiac Autonomic Neuropathy

An abnormal response to any of the three autonomic function tests:

1) **Abnormal Expiration to Inspiration (E/I) ratio:** Mean of longest R-R intervals on ECG during expirations divided by mean of shortest R-R intervals during inspirations over 1 minute. A value less than age- related reference value is abnormal.

   Lowest normal value of E/I ratio: Age 20-24 years(1.17); 25-29(1.15); 30-34(1.13); 35-39(1.12); 40-44(1.10); 45-49(1.08); 50-54(1.07); 55-59(1.06); 60-64(1.04); 65-69(1.03); and 70-75(1.02)

2) Abnormal Heart rate response to postural change:

Longest R-R interval during beats 20-40 after standing divided by shortest R-R interval during beats (ECG) 5-25 after standing. A value less than 1.03 is abnormal.

3) **Abnormal Valsalva ratio:**

Longest R-R interval divided by shortest R-R interval within 45 seconds after forced exhalation into the mouth piece of sphygmomanometer to 40 mm Hg for 15 seconds. A value less than 1.2 is abnormal.

DATA COLLECTION PROCEDURE

The study was conducted after approval from hospitals ethical and research committee. The patients

Table 1: Diabetes duration age groups Cardiac autonomic neuropathy Crosstabulation

			Cardiac autonomic neuropathy		
			Yes	No	Total
s duration ups	10-15 years	Count % within Diabetes duration age groups	36 35.6%	65 64.4%	101 100.0%
	16-20 years	Count % within Diabetes duration age groups	8 61.5%	5 38.5%	13 100.0%
	above 20 years	Count % within Diabetes duration age groups	10 76.9%	3 23.1%	13 100.0%
		Count % within Diabetes duration age groups	54 42.5%	73 57.5%	127 100.0%

uded in the study through OPD and were to the Medical-A Unit Hayatabad Medical for further evaluation. All patients meeting the criteria with fasting blood glucose of > with history of intake of hypoglycemic drugs imum duration of 10 years were included in . The purpose and benefits of the study were to the patients and a written informed con- obtained.

patients were worked up with detailed his- examination and routine investigation. This exclude conditions mentioned in the exclu- to control confounding variables and bias results. All patients were subjected to stan- ECG and respective measurements were for E/I ratio, heart rate response to postural and Valsalva ratio to detect Cardiac Autonomic thy. All the diagnostic procedures were per- by an expert cardiologist with minimum of 5 experience. All the above mentioned informa- uding name, age, gender and address were in a predesigned proforma.

NALYSIS

ta was collected through specially designed and were analyzed using SPSS version 10. ies, percentages were calculated for categori- bles like gender and Cardiac Autonomic Neu- Mean ± SD was calculated for quantitative like age and duration of diabetes. Cardiac ic Neuropathy was stratified among age, gen- duration of diabetes to see the effect modifi- l results were presented in form of tables and

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otal of 127 patients of type 2 diabetes mellitus olled in this study. CAN was present in 54 ype 2 DM patients, the rest 73 (57.5%) showed normal tests for cardiac autonomic neuropathy (Graph No.1). Among these 36 (36.6%) were in 10-15 years duration group, 8(61.5%) patients were among those with 16-20 years duration group. The highest (76.9%) frequency of CAN was present in 10 patients having diabetes for more than 20 years (Table No.1).

The mean age of the sample was 53.08 ± 7.85 years ranged from 35 to 68 years. The maximum patients 51(40.2%) were in 46-55 years followed by age group 56-66 years (33.9%). younger patients 35-45 years constituted 20.5% while the oldest in the sample were only 5.5% of the total type 2 DM patients (Table 1). The mean duration of DM was 13.83 ± 3.48 years. 101 (79.6 %) patients were 10-15 years duration group. 13 (10.2%) were 16-20 years while 13 (10.2%) were in more than 20 years duration group (Table 1). Gender stratification is clear from (Graph No.2). CAN was positive in 70 (56.1%) male and 57 (44.9%) female diabetic patients with male to female ratio of 1.2:1 (Table No.2).

Table 2: Gender Cardiac autonomic neuropathy Crosstabulation

			Cardiac autonomic neuropathy		
			Yes	No	Total
Gender	Male	Count % within gend	29 41.4%	41 58.6%	70 100.0%
	Female	Count % within gend	25 43.9%	32 56.1%	57 100.0%
Total		Count % within gend	54 42.5%	73 57.5%	127 100.0%

Table 3: Age distribution among different diabetic patients

Age of patient in years	Frequency	Percent	Cumulative percent
35-45	26	20.5	20.5
46-55	51	40.2	60.6
56-66	43	33.9	94.5
>66	7	5.5	100.0
Total	127	100.0	

Table 4: Diabetes duration age groups

	Frequency	Percent	Cumulative %
Valid 10-15 years	100	78.7	78.7
16-20 years	13	10.2	89.0
above 20 years	14	11.0	100.0
Total	127	100.0	

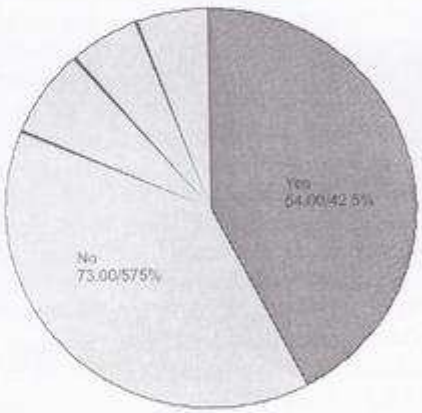

Fig. 1: Cardiac autonomic neuropathy in type 2 diabetes mellitus

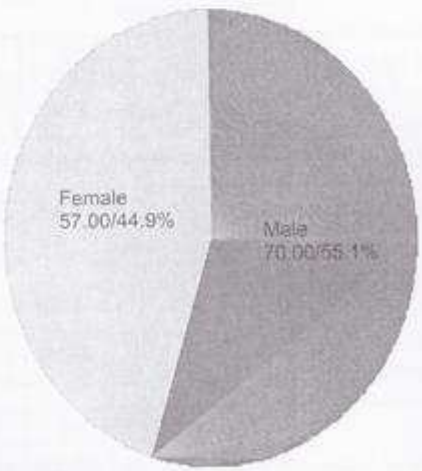

Fig. 2: Gender distribution

DISCUSSION

Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes[11]. A subtype of the peripheral polyneuropathies that accompany diabetes, DAN can involve the entire autonomic nervous system (ANS). ANS vasomotor, visceromotor, and sensory fibers innervate every organ. DAN may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal [GI], genitourinary, sudomotor, or ocular)[13]. Many organs are dually innervated, receiving fibers from the parasympathetic and sympathetic divisions of the ANS. DAN typically occurs as a system-wide disorder affecting all parts of the ANS. Indeed, because the vagus nerve (the longest of the ANS nerves) accounts for 75% of all parasympathetic activity, and DAN manifests first in longer nerves, even early effects of DAN are widespread.

The frequency in our study is 42.5% which is compatible with recent studies like Basu et al [13]. The frequency of CAN was 54% in there study. The reason of this higher frequency is due to very small sample size of fifty patients.

Another study conducted in diabetic patients showed CAN frequency of 60%[19]. Here again one can find the very small sample size of hundred patients. Apart from this,it also included type 1 along with type 2 diabetic patients for detecting the frequency. The frequency of this complication of DM is different in the two types of DM. It is less common in type 1 diabetes than type 2 as the later remains undiagnosed for many years[23].

A recent study conducted in Pakistan has found 30% of CAN in type 2 DM[6]. The setting of this study is a tertiary care hospital but the duration of the study is two months lesser than our study with a small sample size of fifty type 2 DM patients. Apart from these drawbacks the exclusion and inclusion criteria differ from our study. For instance many patients in this study were suffering from cataracts (poor vision), which is a confounding variable and affects the results of such type of study which needs the cooperation and good vision of the patients. Another, Romanian study[20] published last year has shown the CAN prevalence of 62.26% in type 2 DM. The studysample was drawn from local population and was having more than 70% of obese patients with high BMI over 30 kg/m^2. The selection of sample in our study was better than this study. Patients from the whole province and both obese and thin with variable BMI were included in the sample.

The mean age of the study 53.08±7.8 years is compatible with results of recent studies. The mean age of our study differ slightly from a local study[6] where it is 53.62±8.30 years but with a small sample size

The mean age of patients was 52.0±5.10 years in another study[24] compatible with our results because the sample size was closer to our sample size as compared to Basu AK et al[22] and Khoharo HK et al[6] where small sample size and very young patients of 21 years were also included in the study as compared to our study we included patients above thirty five years with minimum duration of 10 years of type 2 DM. It is well known that higher age and longer duration of DM has strong association with CAN[19]. The fact that CAN is common in higher age group has been found in many Pakistani international studies[19,22-24]. The Romanian[25] study has not included any patient above 60 years that is the reason the duration of DM has not exceeded above 20 years. For a study to look into the prevalence of CAN in higher age group the range of age should be wide enough. The rationale such population is very small in number, is that DM is a chronic debilitating disease[25,26] involving almost every system of the body. The life expectancy of diabetic patient is lower than normal healthy population.[26] The lack of awareness and health care facilities in the developing countries like Pakistan make it further difficult to control or prevent diabetic complications like CAN and maintain normal life expectancy.

We did not find any significant relation of CAN with gender. Male to female ratio was matching the results of other local and international studies[19,22-24]. The male to female ratio was 1:1 in local Pakistani study[6] but the sample size and duration of study are far less than our study. Rest of the studies[19,24] has shown slight male predominance for CAN as in our study.

CAN is common in long standing DM, at least 10 year duration of diabetes[19,22,23,24]. In our study > 20 years duration group patients have highest frequency as compared to 10-15 years and 16-20 years duration groups. It is compatible with the fact that longer the duration of DM greater would be the frequency of CAN as it increases from group 16-20 years to above 20 years group patients in this study. The frequency of CAN for duration of DM varies in different studies[23,24]. In these studies the sample size was only fifty and hundred patients respectively with minimum age of 21 years for type 2 DM in the former and no patient above 20 years duration group for DM in the later was included to be able to comment on longer duration of type 2 DM above 20 years and CAN association.

Like other local and international studies[19,22,23,24] we in our study diagnosed CAN with standard reflex test for autonomic dysfunction in diabetic patients, i.e abnormal E/I ratio, abnormal heart rate response to postural change of <1.03 and abnormal valsalva ratio of <1.2. The prevalence of CAN in the community, hospital and clinics based studies varies widely. The true picture of CAN prevalence would be better estimated and analyzed in a large community population based study with more cheaper and more sensitive screening tests. As type 2 DM is increasing rapidly in our part of the world due to poor life style, lack of awareness and late consultation for the symptoms of DM, this complication needs to be evaluated in every type 2 diabetic patient in clinics and hospitals.

CONCLUSION

Cardiac autonomic neuropathy is very common in type 2 diabetes mellitus. Its prevalence is common in patients suffering from DM for more than 10 years. It results in increased morbidity and mortality. Thus every type 2 diabetic patient should be screened for cardiac automatic neuropathy.

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