

# Frequency of Cardiac Autonomic Neuropathy and its Various Grades in Type 2 Diabetes Mellitus

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## ABSTRACT

**Introduction:** Cardiovascular autonomic neuropathy (CAN) is a common and one of the major complication of diabetes mellitus. It is also the most under diagnosed and least understood diabetic complication<sup>4</sup>.

**Objective:** To determine the frequency of cardiac autonomic neuropathy and its various grades in type 2 diabetes mellitus.

**Study Design:** Cross Sectional Study.

**Setting:** Medical OPD as well as from diabetic clinic of Services Hospital, Lahore.

**Methodology:** Total 195 patients of either sex or age between 18 to 60 with at least 10 years duration of type 2 Diabetes Mellitus were enrolled. Cardiac Autonomic Neuropathy was determined using Ewing's criteria. Frequency of CAN and its severity grades was recorded.

**Result:** Mean age of sampled population was  $54.42 \pm 2.925$  ranged from 44 to 60 years. There were 77 (39.5%) female and 118(60.5%) patients (60.5%) were male. Out of 195, 99 (50.8%) patients had cardiac autonomic neuropathy, 34 (17.4%) patients had early, 56 (28.7%) had definite, 8 (4.1%) had severe & 1 patient had atypical cardiac autonomic neuropathy. It was associated with advancing age but gender and duration of diabetes had no effect.

**Conclusion:** The study concludes that frequency of cardiac autonomic neuropathy is quite high (50.8%) in patients with more than ten years duration of type II diabetes. Thirty four (17.4%) had early level, 56 patients (28.7%) had definite, 8 patients (4.1%) had severe and 1 patient had Atypical cardiac autonomic neuropathy.

**Keywords:** Cardiac Autonomic Neuropathy, Diabetes, Insulin resistance, Autonomic instability, Neuropathy

## INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia<sup>1</sup>. It currently assumes a pandemic status, with global prevalence of 366 million in 2011 and expected rise to 552 million by 2030<sup>1</sup>. In Pakistan prevalence of (DM) ranges from 7.6 to 11%<sup>2,3</sup>.

Cardiovascular autonomic neuropathy (CAN) is a common and the major complication of diabetes mellitus. It is also the most under diagnosed and least understood diabetic complications, that can lead to a diverse spectrum of clinical manifestations ranging from impairment of exercise intolerance to sudden cardiac death<sup>4,5</sup>.

The prevalence rates for CAN is variable. This is due to difference in criteria used, variable diagnostic procedures and difference in patient cohort either community based study or referral center study. The reported prevalence ranges from 7.7% in newly diagnosed diabetics to as high as 90% in potential recipients of a pancreatic transplant<sup>6</sup>.

On average, autonomic neuropathy complicates diabetes mellitus 10 years following the onset of diabetes and is slowly progressive<sup>11</sup>. For the past two decades, it had already been demonstrated that CAN is significantly associated with overall mortality and morbidity such as silent myocardial ischemia, left ventricular systolic and particularly diastolic dysfunction in the absence of cardiac disease, coronary artery disease, stroke, diabetic nephropathy progression, and perioperative morbidity<sup>7-9</sup>. Since clinical history & physical examination are ineffective for its primary detection it is of crucial importance to perform quantitative tests in order to diagnose CAN in its initial & still reversible stages<sup>16</sup>. The tests recommended by American Diabetes Association are Ewing's tests and computerized heart rate variability study<sup>10</sup>.

Keeping in view the burden of the CAN, its impact on management of diabetes as a whole and the fact that there is real possibility of returning its natural course, the early diagnosis is crucial<sup>12</sup>. This study will be conducted to know about the frequency of CAN in diabetes as well as its various grades of severity, using Ewing's tests that are simple, non-invasive, reproducible sensitive and could be performed in resource poor setting commonly encountered in Pakistan. The previous local studies revealed 16%,

28%, and 10% early, definite and severe CAN<sup>7</sup>, 30% and 40% borderline and definite CAN in type 2 diabetics<sup>8</sup>, previous studies took patients irrespective of the duration of diabetes, but in this study we will take patients having diabetes of more than 10 years duration.

## MATERIAL AND METHODS

The cross sectional study was conducted from July 2021 to December 2021 at medical OPD as well as from diabetic clinic of Services Hospital, Lahore. Sample size was calculated with 95% Confidence Level, 7% desired absolute precision (d), taking expected percentage of 54%.

All type 2 Diabetes mellitus patients of both genders and age more than 18 years but less than 60 years, and 10 years or more of Diabetes duration were included.

Patient with Diabetes mellitus and Co-morbidities on history, medical record or as defined by standard terms, cardiac failure (Echo showing E.F<50%), chronic Kidney Disease (eGFR<60ml/min), chronic liver disease (ALT> 2times normal), Anemia (Hb<11g%) were excluded.

Demographic data such as age, gender, address, brief history regarding duration of Diabetes, treatment taken was recorded. All patients underwent ECG, Fundoscopy, RFTs, LFTs, Echocardiography, Ewing's tests. Ewing's tests required: a sphygmomanometer, a 5ml syringe and an ECG machine. Patients advised to avoid caffeine, nicotine four hours prior to test. ECG electrodes firmly attached to the patient chest:

- Patient blew in to the plunger end of 5 ml syringe attached to mercury sphygmomanometer till it remained at 40mmHg for 15 seconds,
- We measured shortest R-R interval during maneuver and longest R-R interval immediately after the maneuver.
- Then we asked the patient to breathe deeply measure max and min R-R interval for each cycle and converts to beats/ min.
- Result were the mean difference (max-min) for heart rate.
- Start ECG with patient lying
- Ask the patient to stand, calculate longest/shortest ratio at 15th and 30th beat.

- Blood pressure of the patient were measured in supine and standing position.
- The Sphygmomanometer cuff was used for handgrip against pressure of 60 mmHg, then at one third of it. The blood pressure recorded thrice before and one minute interval during hand grip from non-exercising hand. The difference between the highest Diastolic Blood pressure during handgrip and mean of three Diastolic Blood pressure readings before handgrip began were taken.
- Frequency of CAN and its severity grades were the outcome variable and recorded as per operational definition.

**Data Analysis:** Data was analyzed in SPSS 25 version. Age & duration of diabetes mellitus was presented by calculating mean & SD, whereas Gender, CAN & grades tests, were presented in form of frequency and percentage. Chi square test was used post stratification and a p-value <0.05 was considered statistically significant. Data was stratified for age, gender and duration of diabetes type 2 to deal with effect modifiers.

**RESULTS**

Total 195 patients were included. The mean age was 54.42 ± 2.925 ranged from 44 to 60 years. There were 119(61%) patients below 55 years of age whereas 76(39%) patients were either 55 years or above. There were 77(39.5%) were male and 118(60.5%) were female. Table: 1

Table 1: Demographic and other parameters in patients

	Mean+ SD	Frequency (%)
Age	54.42+ 2.92	
	Below 55years	119(61%)
	55 or above	76(39%)
Gender	Female	77(39.5%)
	Male	118(60.5%)
Cardiac Autonomic Neuropathy	Yes	99(50.8%)
	No	96(49.2%)

Out of 195, 99(50.8%) patients showed cardiac autonomic neuropathy. In 99 cardiac autonomic neuropathic patients, 34(17.4%) patients were having early level, 56(28.7%) patients were having definite, 8(4.1%) patients were having severe and only 1(%) patient was having Atypical level of severity of cardiac autonomic neuropathy. The mean duration of diabetes was 12.91 ± 1.059. Among 99 cardiac autonomic neuropathy patients, 38 were female and remaining 61 patients were male. Table: 2

Table 2: Descriptive of Severity of Cardiac Autonomy Neuropathy

	Frequency (%)	
Severity of Cardiac Autonomy Neuropathy	No	96(49.2%)
	Early	34(17.4%)
	Definite	56(28.7%)
	Severe	8(4.1%)
	Atypical	1(0.5%)

Data was stratified according to gender, 38 females and 61 males had cardiac autonomy neuropathy. The result was insignificant. (P> 0.05) Data was stratified according to age group with cardiac autonomic neuropathy, the results were significant (p=0.001). Out of 99 cardiac autonomic neuropathy patients 49 patients were below 55 years and 50 patients were either 50 years or above. There were 37 patients below 12 years of diabetes duration and 62 were above 12 years of Diabetes duration that had cardiac autonomy neuropathy. The result was also insignificant. Table: 3

Among 38 cardiac autonomic neuropathy female patients severity level was early in 12 females, definite in 23 and severe in 3 female patients. However in 61 cardiac autonomic neuropathy male patients, Twenty two patients had early, 33 patients had definite, 5 patients had severe and Atypical in only 1 patient. Results were non-significant (p=0.906). Table: 4

Table 3: Cardiac Autonomy with Gender, Age, Duration of Diabetes

		Cardiac Autonomy Neuropathy		P value
		Yes	No	
Gender	Female	38	39	0.75
	Male	61	57	
Age Groups	Below 55 years	49	70	0.001
	55 years or above	50	26	
Duration of Diabetes	Below 12 years	37	30	0.36
	12 years & above	62	66	

Age groups with severity of cardiac autonomic neuropathy, results were significant (p=0.001). Among 49 below 55 years' cardiac autonomic neuropathy patients, severity level in 15 patients were early, in 33 patients had definite and in 1 patient it was severe. While severity level in patients 55 years or above, 19 patients were having early level, 23 were having definite, 7 were having severe and 1 was atypical. Table: 4.

Table 4: Age groups with severity of cardiac autonomic neuropathy

		Severity of Cardiac Autonomy with Gender, Age and Duration of Diabetes					P value
		No	Early	Definite	Severe	Atypical	
Gender	Female	39	12	23	3	0	0.90
	Male	57	22	33	5	1	
Age Groups	Below 55 yrs	70	15	33	1	0	0.001
	55yrs or above	26	19	23	7	1	
Duration of Diabetes	Below 12 ys	30	15	20	2	0	0.64
	12 yrs or above	66	19	36	6	1	

**DISCUSSION**

Cardiac autonomic neuropathy is the leading cause of silent cardiovascular events in those who don't have any signs or symptoms of heart disease. The high frequency of CAN among newly diagnosed T2D patients shows that its pathogenesis is rooted in a more advanced stage of metabolic dysfunction, such as prediabetes<sup>11,12</sup>.

In our study, 99 patients (50.8%) had cardiac autonomic neuropathy according to operational definition. In 99 cardiac autonomic neuropathic patients (50.8% of total population), 34 patients (17.4%) were having early level, 56 patients (28.7%) were having definite, 8 patients (4.1%) were having severe and 1 patient was having Atypical level of severity of cardiac autonomic neuropathy. The prevalence rates for Cardiac Autonomic Neuropathy are variable.

Our results match with those reported in one of the recent research, in which prevalence of Cardiac Autonomic Neuropathy was found to be 54%, with 16% early CAN, 28% and 10% had definite and severe CAN<sup>13</sup>. In 2017 study, showed that the frequency of CAN in type II diabetics and found definite and borderline CAN in 30% and 40% patients respectively<sup>14</sup>. M Safi et al. conducted a study on prevalence of Autonomic Neuropathy in poorly controlled diabetics and found CAN in 43% patients<sup>15</sup>. Another study, showed that all patients had CAN – 14.53% had early, 26.66% had definitive & 59.67% had severe CAN<sup>16</sup>.

Ekta K et al. conducted a study to assess the pattern and prevalence of CAN in diabetics and revealed that 80.64% patients had CAN with 34.67% have abnormal deep breathing test, 45.90% have abnormal hand grip, 17.35% have abnormal orthostatic hypotension, making 11% early 0% definite, 20% severe and 69% in atypical grade of CAN<sup>17</sup>.

Discrepancy that exists between local and international literature is on the magnitude of early and definite CAN which were found to be high in local studies, while severe CAN grades was high in international studies. Similarly Atypical grade for CAN was not used by local studies.

## CONCLUSION

The study concludes that frequency of cardiac autonomic neuropathy is quite high (50.8%) in patients with more than ten years duration of type II diabetes, 34 patients (17.4%) had early level, 56 patients (28.7%) had definite, 8 patients (4.1%) had severe and 1 patient had Atypical cardiac autonomic neuropathy. Limitations of study include smaller sample size along with non-representative sample from a tertiary care hospital.

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