Original Article

Frequency of Silent Myocardial Ischemia in Type 2 Diabetic Patients Having Cardiovascular Autonomic Neuropathy

Ghulam Abbas Sheikh, Masood Javaid, Dilshad Muhammad, Rahmat Ullah

ABSTRACT

Introduction: Early detection of silent myocardial ischemia plays an important role in prevention of sudden cardiac death and acute myocardial infarction. The studies regarding the frequency of silent myocardial ischemia in diabetic patients having cardiovascular autonomic neuropathy are few so we planned this study to determine the frequency of silent myocardial ischemia among patients with diabetic cardiovascular autonomic neuropathy in our population. **Objectives**: To determine the frequency of silent myocardial ischemia in type 2 diabetic patients having cardiovascular autonomic neuropathy. **Study Design:** Cross-Sectional study. **Place and Duration of Study:** Medical Departments of Allied Hospital and Aziz Fatimah Hospital Faisalabad from 01-08-2013 to 31-01-2014. **Methods:** This study included 91 type 2 diabetic patients with cardiovascular autonomic neuropathy. All the patients had ECG done. Those who had normal ECG underwent ETT, to determine if there was any silent myocardial ischemia which was described as frequency distribution table. The data was collected on specially designed performa. **Results:** Total 91 patients were included in the study. Silent myocardial ischemia was present among 35 (38.5%) patients while 56 (61.5%) did not have silent myocardial ischemia. The mean age of the patients was 52.99 $\pm$ 7.00 years [range 41-71years]. 57 (62.6%) patients were male and 34 (37.4 %) patients were female. ECG was positive for ischemia among 25 (27.5%) patients and ETT was positive for ischemia among 10 (11%) patients. **Conclusion:** The frequency of the silent myocardial ischemia is high among patients with diabetic cardiovascular autonomic neuropathy, so every diabetic patient with cardiovascular autonomic neuropathy should be screened for ischemic heart disease. **Keywords**: Diabetes mellitus; cardiovascular autonomic neuropathy; silent myocardial ischemia

INTRODUCTION

Diabetes Mellitus (DM) is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or to a combination of insulin resistance and inadequate insulin secretion to compensate.[1] The prevalence of diabetes mellitus for all age groups worldwide was estimated to be 2.8% in year 2000 but it will increase to 4.4% by the year 2030.[2]

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No accurate figures for the prevalence of diabetes mellitus in Pakistan are available but according to several small scale studies conducted in different parts of country prevalence of diabetes mellitus vary from 5.3% to 16.2%.[3] The prevalence of diabetes mellitus has increased dramatically in the past two decades. It is estimated that the number of diabetic patients will grow from 135 million to 300 million by the year 2025 in the world. Unfortunately the major increase will occur in developing countries, and in Pakistan the number of diabetic patients in year 2025 is estimated to be doubled. In Pakistan approximately 8 million people have diabetes mellitus and same number is suffering from impaired glucose tolerance.[4] In USA prevalence of diabetes mellitus is 9.3%,[2] and it has been seen that 11% people with diabetes mellitus were unaware of their disease and 8%

were found to have Impaired Glucose Tolerance (IGT).[5]

One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics.[6]

Diabetes mellitus has been found to increase the risk of ischemic heart disease (IHD).[7] Coronary artery disease accounts for 80 percent of mortality in type 2 diabetics.[8] In fact, the American Heart Association and European Society of Cardiology both consider type 2 diabetes as an equivalent of coronary heart disease.[9,10]

Silent myocardial ischemia (SMI) is defined as the presence of objective evidence of myocardial ischemia, in the absence of chest pain or other angina equivalents. Silent ischemia is associated with an increase in coronary risk that may be reversible with appropriate therapy. Sudden death is the initial manifestation of coronary disease in 18% of coronary events[11] and more than one-half of sudden deaths occur without a prior history of coronary heart disease.[12]Diabetic patients have higher prevalence of silent myocardial ischemia and unrecognized myocardial infarction than patients without diabetes.[13, 14] The exact reasons for the development of angina during some episodes of myocardial ischemia and absence of symptoms during other episodes are not known. Some mechanisms include:

1. Inability to reach pain threshold during an episode of ischemia,
2. Lesser severity and shorter duration of ischemic episodes,
3. Presence of higher threshold for pain,
4. Generalized defective perception of painful stimuli,
5. Presence of a defective angina warning system,
6. Higher beta-endorphin levels and higher production of anti-inflammatory cytokines which block pain transmission pathways and increase threshold for nerve activation. Autonomic neuropathy involving cardiac afferent nerves in diabetes mellitus might account for the higher incidence of silent ischemia in diabetics.

Cardiovascular autonomic neuropathy is a common form of autonomic neuropathy, causing abnormalities in heart rate control and central and peripheral vascular dynamics. Cardiovascular autonomic neuropathy has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular liability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction. Cardiovascular autonomic neuropathy occurs in 17 % of patients with type 1 diabetes and 22 % of those with type 2. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction.[15] The prevalence of cardiovascular autonomic neuropathy increases in direct proportion to age, duration of diabetes mellitus and poor glycemic control.[16]The prevalence of silent myocardial ischemia in diabetics having cardiovascular autonomic neuropathy is 37.6%.[17]

Despite its potential negative impact on the quality of life of patients, cardiovascular autonomic neuropathy, is the least understood and diagnosed complications of diabetes mellitus. Cardiovascular autonomic neuropathy is subdivided into subclinical (in which functional and reversible alterations are present) and clinical (when structural neuronal alterations are present): the first one is only diagnosed by tests and may occur as soon as the diagnosis of certain types of DM is made, or in the early years of the disease; the second form, as the name suggests, is symptomatic and occurs in more advanced stages.[18]

Autonomic fibers are compromised in the several clinical subtypes of diabetic neuropathies. The most common type, classical peripheral neuropathy (symmetric, distal, and predominantly sensory), shows a strong correlation with autonomic neuropathy, and 50% of the diabetic patients with peripheral neuropathy have asymptomatic cardiovascular autonomic neuropathy, whereas 100% of those with symptomatic cardiovascular autonomic neuropathy have classical peripheral neuropathy.[19,20]

Different diagnostic tools are used to identify silent myocardial ischemia. No single test is ideal for screening patients for silent myocardial

ischemia. A 12 lead electrocardiography (ECG) and exercise treadmill test (ETT) are useful for diagnosis of silent myocardial ischemia in diabetics.[21] Both are economical and readily available tools at tertiary care setup.

Identification of SMI is of great value in clinical practice. Due to lack of ischemic symptoms, diabetic patients having cardiovascular autonomic neuropathy remain unaware about long standing ischemia. They present late to benefit from thrombolytic therapy and there is high rate of cardiac arrhythmias and sudden cardiac deaths in diabetics. The aim of our study is to identify these cases of silent myocardial ischemia and motivate our colleagues to conduct simple bedside cardiac autonomic function tests more commonly and increase their index of suspicion about silent myocardial Ischemia in type 2 diabetic patients. In this way we can decrease and prevent the dreadful cardiovascular outcomes of unrecognized silent myocardial ischemia and decrease the hospital admissions and burden on our already limited resources.

OPERATIONAL DEFINITIONS

Silent Myocardial Ischemia (SMI):

Patients with objective signs of ischemia or MI (myocardial infarction) on ECG or having positive ETT but no chest pain were considered as having SMI.

Following ECG criteria were used to diagnose ischemia or MI:

Definite MI: Q-wave > R/3 and Q-wave duration > 0.03 sec. in all leads except iii and aVR.

Ischemia: ST-segment depression/elevation > 1mm, or flat, negative or biphasic T-wave with negative phase < 1mm, or negative T-wave > 5mm in any lead, or complete LBBB.

Diabetes Mellitus (DM):

Type 2 DM patients were defined as:

1) Already diagnosed and on treatment for DM,

2) Random blood glucose level ≥ 200 mg/dl on 2 or more occasions,

3) Fasting glucose level ≥ 126mg/dl on 2 or more occasions. Duration of type 2 DM was defined as the time lapse from diagnosis to the time of IHD testing, measured in years.

Cardiovascular Autonomic Neuropathy (CAN):

Patients having ≥ 2 of the following cardiovascular autonomic function tests positive were considered as having CAN**:** Heart rate response to valsalva maneuver (RR at rest/RR during valsalva) <1.10, heart rate variation during deep breath (exp: insp ratio) <1.00, heart rate response to standing (30^{th}-15^{th} beat ratio) <1, systolic blood pressure response to standing >30mmHg, diastolic blood pressure response to sustained hand grip <10mmHg.

MATERIALS & METHODS

Study design

Cross sectional study

Place of Study

Medical departments of Allied hospital and Aziz Fatimah hospital Faisalabad.

Sample size

Our sample size as calculated using WHO calculator with 95% confidence level and 10% margin of error, Sample size (n) = 91

Sample technique

Non probability purposive sampling

Duration of Study:

Six months from 01-08-2013 to 31-01-2014

Inclusion criteria

All patients with type 2 diabetes:

1. Having cardiovascular autonomic neuropathy.
2. Of more than 5 years duration.
3. Both men and women of age ≥ 40 years.
4. With no history of chest pain.

Exclusion criteria

1. All patients of type 1 diabetes.
2. All patients already known to have IHD or valvular heart disease
3. All patients with cardiac failure (clinically presence of raised JVP, pedal edema, S_3 gallop, basal fine crepitations in lungs)
4. All patients on chronic medication with drugs known to cause ST segment or T wave changes (especially Digoxin and Diuretics), or to affect autonomic function.

Data Collection

Type 2 diabetics both from outpatient and inpatient departments were enrolled according to inclusion and exclusion criteria. We took informed written consent from patients after fully explaining the purpose and benefits of our study. We took detailed history, performed complete

physical examination and checked all available medical record of patients. Cardiac autonomic function tests were conducted on all patients and interpreted as described in operational definitions. Fasting and random blood sugar levels and resting state ECG was done in all patients and evaluated by criteria described in operational definitions. Patients found to have negative ECG for myocardial ischemia were referred for ETT to cardiology department of hospital. ETT was performed using Bruce protocol and was supervised and reported by cardiologist. Those patients who had normal ECG and ETT were considered negative for SMI, while those patients who had ischemic changes on resting state ECG or whose ETT was positive, were labeled as having SMI.

Data Analysis

The data was analyzed by using SPSS version 10. Mean and standard deviation was calculated for quantitative variables i.e. age of patients, duration of diabetes and no. of positive autonomic function tests. Frequency and percentages for all qualitative variables gender and SMI on ECG and ETT were calculated. The results were presented in tables and figures as appropriate.

RESULTS

There were total 91 patients included in the study.

Distribution of patients by age:

The mean age of the patients was 52.99 + 7.00 years [range 41-71years]. There were 16 (17.6%) patients of age range of 40-45 years, 15 (16.4%) patients of age range of 46-50 years, 21 (23.1%) patients of age range of 51-55 years, 33 (36.3%) patient of age range of 56-60 years and 6 (6.6%) patients were above 60 years of age. (Table 1)

Distribution of patients by sex:

Out of 91 patients included in the study, 57 (62.6%) patients were male and 34 (37.4 %) patients were female. The male to female ratio in this study was 1.7:1. (Figure 1)

Distribution of patients by the number of positive tests for autonomic neuropathy:

There were 49 (53.8%) patients in whom 2 tests were positive for autonomic neuropathy. Three, four and five tests for autonomic neuropathy were positive among 25 (27.5%), 12 (32.2%) and 5 (5.5%) patients, respectively. (Table 2)

Distribution of patients by the type of positive tests for autonomic neuropathy:

HR response to Valsalva maneuver was positive among 86 (94.5%) patients, HR response on deep breath was positive among 65 (71.4%) patients, HR response to standing was positive among 57 (62.6%) patients, systolic BP response to standing was positive among 21 (23%) patients and diastolic BP response to hand grip was positive among 12 (13.2%) patients. (Table 3)

Distribution of patients by ECG and ETT test for Ischemia:

ECG was positive for ischemia among 25 (27.5%) patients, ETT was positive for ischemia among 10 (11%) patients and ECG and or ETT was normal among 56 (61.5%) patients. (Table 4)

Distribution of patients by silent ischemia:

Silent ischemia was detected among 35 (38.5%) patients and 56 (61.5%) patients did not have ischemia. (Figure 2)

Table 1: Distribution of patients by age
(n=91)

Age (years)	No. of patients	Percentage
40-45	16	17.6
46-50	15	16.4
51-55	21	23.1
55-60	33	36.3
> 60	6	6.6
Mean $\pm$ SD	52.99 $\pm$ 7.00	
Range	41-71	

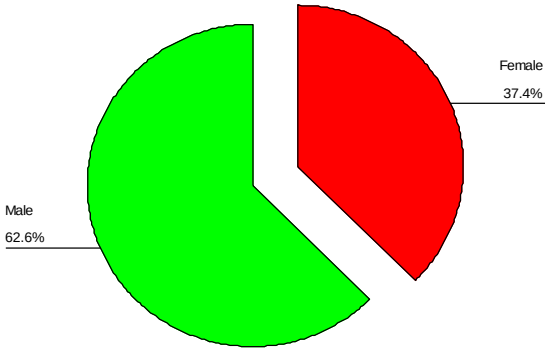

Figure 1: Distribution of patients by sex (n=91)

Table 2: Distribution of patients by the number of positive tests for autonomic neuropathy (n=91)

No. of Positive Autonomic neuropathy	No. of patients	Percentage
2	49	53.8
3	25	27.5
4	12	13.2
5	5	5.5
Total	91	100

Table 3: Distribution of patients by the type of positive tests for autonomic neuropathy (n=91)

Type of positive test for Autonomic neuropathy	No. of patients	Percentage
HR response to Valsalva maneuver	86	94.5
Hr variation on deep breath	65	71.4
HR response to standing	57	62.6
Systolic BP response to standing	21	23
Diastolic BP response to hand grip	12	13.2

Table 4: Distribution of patients by ECG and ETT test for Ischemia (n=91)

Test	No. of patients	Percentage
ECG Positive for ischemia	25	27.5
ETT positive for ischemia	10	11
Normal ECG / ETT	56	61.5

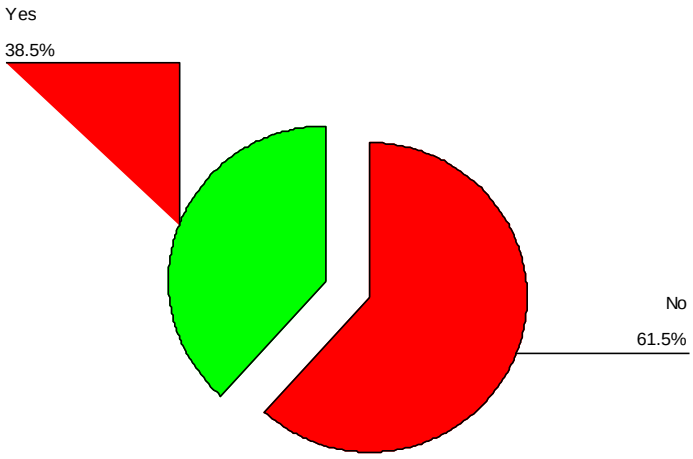

Figure 2: Distribution of patients by silent ischemia (n=91)

DISCUSSION

In this prospective clinical study, we studied 91 diabetic patients with diagnosis of cardiovascular autonomic neuropathy. We investigated these patients to determine the frequency of silent myocardial ischemia. The results of this study showed a higher frequency of silent myocardial ischemia (38.5%) in type 2 diabetics with cardiovascular autonomic neuropathy. This study also proves that routine ECG or ETT are helpful to detect the silent myocardial ischemia among diabetic patients.

In literature, there are studies that have described the frequency of silent myocardial ischemia among diabetic patients with cardiovascular autonomic neuropathy. However, the results of

these studies are variable because of different methodology and criteria used.

Negrusz Kawecka M, [22] conducted a study of 67 patients with diabetes mellitus without clinical symptoms of ischemic heart disease. The average duration time of diabetes mellitus was 11 years, and 41 patients had type 2 and 26 patients had type 1 diabetes mellitus. 24-hours ambulatory Holter monitoring and ETT were performed in all subjects. The diagnosis of silent myocardial ischemia was established in patients with positive results of both tests without any chest pain. In case of only one positive result, the dipyridamole stress echocardiography test with ECG was carried out to prove the diagnosis. It was proved, that silent myocardial ischemia occurred in 22% type 2 diabetic patients. They recommended the use of 24-hours Holter monitoring combined with ETT and dipyridamole stress echocardiography to detect silent myocardial ischemia. Our study established the diagnosis of ischemia on ECG and ETT and revealed high prevalence of silent myocardial ischemia compared to their study. This may be due to selection of only those diabetics who had cardiovascular autonomic neuropathy and difference of diagnostic tools applied in both studies.

May O, et al, [23] performed a study among diabetic patients to find out the prevalence of silent myocardial ischemia. They included 120 patients with type 2 diabetes mellitus. The patients included were in age range of 45 – 70 years. ST-depression of horizontal or descending character of at least 0.1 mv measured 80 ms after the J-point on either exercise ECG or Holter ECG was considered indicative of myocardial ischemia. The observed prevalence of silent myocardial ischemia in diabetics was 13.5%. Like our study, they used ECG criteria to detect ischemia; however, the frequency of silent ischemia in our study was higher as compared to this study.

In a study by Balouch GH, et al, [24] 100 patients with type 2 diabetes mellitus were studied. The mean age of the patients was 48.7 $\pm$ 7.2 years compared to 52.99 $\pm$ 7.00 years of our study population. All the patients were tested with ETT to detect ischemia. The results of this study showed that silent myocardial ischemia was present among 37% diabetic patients. The results of this study are similar to that of ours in terms of silent myocardial ischemia and showed that ETT detected more patients with silent ischemia compared to 24 hours Holter monitoring.

In a prospective study by Blandine et al. [25] 203 diabetic patients without angina and with normal resting ECG were evaluated with ETT (stress nuclear imaging was used if ETT was contraindicated or inconclusive). In this study 16% patients had abnormal stress tests compatible with silent myocardial ischemia.

In a study by Bacci et al.[26] which evaluated 206 higher risk asymptomatic type 2 diabetes patients with peripheral arterial disease and at least 2 cardiovascular risk factors, 19% had an abnormal test and the positive predictive accuracy of the exercise ECG was 79%.

In another study by Faghih-Imani et al.[27] a total of 500 subjects (44.4% men and 55.6% women) were studied. The subjects had a mean age of 49.59 years (18-80 years). The resting state ECG was used as diagnostic tool and Minnesota codes for ischemia were used to read ECG. ECG changes favoring MI, probable MI, and ischemia were seen in 2%, 12.4%, and 13.6% of patients respectively. The results of this study with use of resting state ECG only to detect silent myocardial ischemia are comparable to our results 28% and 27.5% respectively.

In our study, we used ECG and exercise tolerance test to diagnose the silent ischemia. The resting ECG, frequently complemented by exercise ECG, assists in cardiac screening of diabetic individuals and helps detect silent ischemia, assess prognosis, and predict mortality.[28] A 12 lead ECG is simple, economical and readily available tool requiring little technical expertise. It picked up a high frequency of silent ischemia in diabetic with cardiovascular autonomic neuropathy. It may be due the selection of specific diabetic patients and the criteria used to read ECG. Exercise tolerance test is readily available, inexpensive and commonly used test used to detect coronary artery disease. It has been well validated in the general population and it can be used as the first diagnostic test for patients with an intermediate risk of having coronary artery disease. Given the differences in presentation of coronary artery disease within the diabetic population and the high

incidence of silent myocardial ischemia, various groups have attempted to evaluate whether exercise ECG has similar accuracy in diabetic population as in general population.

These studies collectively support the notion that among higher risk cohorts of asymptomatic patients with type 2 diabetes nearly 1/3 may have unrecognized coronary artery disease and exercise ECG may be useful in identifying these patients.

Anti-ischemic drug therapy and aspirin reduce the risk of cardiac events in patients with silent ischemia. This has been proved by a study of Paul E and colleagues.[29] In this randomized multicenter trial of 263 patients with silent ischemia identified by exercise treadmill testing (ETT) and stress imaging, 51 patients were randomized to receive antianginal drug treatment and remaining were in control group. Over the next 11 years, only3 patients in the medical treatment group experienced cardiac death, nonfatal MI, or acute coronary syndrome compared with 17 in the control group ($P < .001$).

The association of mortality and cardiovascular autonomic neuropathy indicates that individuals with abnormal autonomic function tests are candidates for close surveillance. Thus it has been recommended that a baseline determination of cardiovascular autonomic function be performed upon diagnosis in type 2 diabetes, and within 5 years of diagnosis for those with type 1 diabetes, followed by a yearly repeat test. In addition, the presence of autonomic dysfunction should alert the health care professional to search for associated risk factors for cardiovascular disease and implementation of an intense program to reduce these factors and thereby reduce the risk of mortality.

Our study had several limitations. First, this study was limited to a specific geographical area. Thus, large-scale studies at multiple centers are necessary to confirm these results. Second, we did not perform further tests in patients with normal ETT. Therefore, some patients with normal ETT might have had asymptomatic myocardial ischemia. Third, given the complex and controversial mechanisms of silent myocardial ischemia, even in the absence of diabetes, further studies are needed to clarify the exact role of cardiovascular autonomic neuropathy in this context.

CONCLUSION

The frequency of silent myocardial ischemia is high among the diabetic patients with cardiovascular autonomic neuropathy. So, it is suggested that all the patients with proven diabetic cardiovascular autonomic neuropathy should be evaluated / screened for the presence of silent myocardial ischemia. Resting ECG and ETT are useful diagnostic tools to detect the ischemia. All the patients should be first screened with ECG and if negative for ischemia, ETT should be done.

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