Original Article

FREQUENCY OF SILENT MYOCARDIAL ISCHEMIA IN PATIENTS WITH DIABETIC NEPHROPATHY

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ABSTRACT

INTRODUCTION: As silent myocardial ischemia (SMI) is more common in diabetic population leading to the development of future coronary artery disease, so its early diagnosis is important. This study was conducted to determine the frequency of silent myocardial ischemia in Type 2 diabetic patients with microalbuminuria.

MATERIAL AND METHODS: This Cross sectional study was conducted at Punjab Institute of Cardiology, Lahore from September 2016 to March 2017. Total 135 patients aged 35- 80 years with type 2 Diabetes Mellitus and having microalbuminuria were enrolled. Their demographic information was noted. Then patients underwent an exercise treadmill test. Silent myocardial ischemia was diagnosed if the test was positive for ischemia in the absence of anginal symptoms.

RESULTS: Mean age of the patients was 61.10±13.52 years, and there were 69 (51.1%) male patients were. Mean body mass index was 30.09±5.70 kg/m2. Mean duration of disease was 12.59±9.18 years. Overall, SMI was seen in 37(27.4%) patients. Patients in the age group 66-80 had the highest frequency of SMI (81.1%). Patients who had SMI, all of them were obese. p-value= 0.000. Duration of disease was also significantly associated with SMI. Age, Gender and smoking status of patients were not significantly associated with SMI.

CONCLUSION: SMI was seen in 27.4% patients. SMI was significantly associated with age, body mass index and duration of diabetes.

KEY WORDS: Silent Myocardial Ischemia, Type 2 diabetes mellitus, Microalbuminuria

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INTRODUCTION

Type II Diabetes mellitus (T2DM) is considered a coronary artery disease equivalent thereby elevating it to the highest risk category. Coronary atherosclerosis is the cause of death in three-fourth of diabetics. Silent myocardial ischemia is a common manifestation of coronary heart disease (CHD) and is more in diabetics.[1] Myocardial ischemia can occur without overt symptoms. In fact, asymptomatic (or silent) ST-segment depression during ambulatory electrocardiogram monitoring occurs more often than symptomatic ST-segment depression in patients with coronary artery disease.[2]

Silent myocardial ischemia (SMI) is more common in diabetic patients than among the general population. It is not yet established whether a routine screening test for SMI is necessary, and which screening test would be most useful.[3] SMI can be diagnosed by conventional cardiac stress testing. Presence of SMI can also be suspected in the presence of microalbuminuria (MAU) because recently it is claimed that MAU is one of the important predictor for cardiovascular disease.[4]

In a study, the reported frequency of SMI was 9.6% in type II diabetic patients with microalbuminuria.[5] Another study showed that prevalence of SMI in T2DM subjects was 13.5%.[6] In another study, the reported frequency of SMI was 34% in type II diabetic patients with microalbuminuria.[7] Another study showed that the frequency of SMI among T2DM patients was 36.8%.[8]

SMI have similar risk factors and increases the risk of future cardiovascular (CV) events. Early detection and intervention can reduce the risk of first Myocardial Infarction (MI) and substantially reduce the risk of further clinical CV events after silent MI.[8]

Rationale of this study was to assess the frequency of silent myocardial ischemia in type 2 diabetic patients with microalbuminuria. Literature has showed that SMI is uncommon in T2DM patients as the frequency is very low [5,6]. But there

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are also controversial evidences in literature which show that SMI may be a risk for development of myocardial infarction [7,8]. Unfortunately, there is no local evidence available to show the extent of the problem in local population. Through this study we want to get the local estimates, so that in future we may be able to implement the results of this study for regular screening of T2DM patients, particularly if patients also develop microalbuminuria. This will improve our practice as well as will also decrease the chances of first MI in these patients. The objective of this study was to determine the frequency of silent myocardial ischemia in type 2 diabetic patients with microalbuminuria.

MATERIALS AND METHODS:

This cross-sectional study was conducted in Department of cardiology, Punjab Institute of cardiology Lahore (PIC) from September 2016 to March 2017. A total of 135 patients were include in the study. Sample size of 135 was calculated with 95%confidence level, 5% margin of error and taking expected percentage of SMI i.e. 9.6% in patients presenting with T2DM. Non-Probability, consecutive sampling tschnique was applied.

Patients aged 35-80 years of age from either gender having T2DM of at least one year duration with microalbuminuria without chest pain or anginal symptoms were enrolled from outpatient department of PIC. Informed consent was obtained from all patients. Diabetes Mellitus was defined if random blood sugar was $\geq$ 200 mg/dl or fasting blood sugar was $\geq$ 126 mg / dl on more than one occasion. Microalbuminuria was established if i.e. albumin 30-300mg/24-hour urine collection. Following were the exclusion criteria: history of using alcohol or narcotics, diagnosis of neuropathy (on medical record), previous history of MI, Fever (>99°F), urinary tract infection (pus cells >3/ HPF in urine culture), pregnancy (on history). All these patients were subjected to standard Exercise Treadmill Test (ETT) on Bruce Protocol. SMI was diagnosed if there was horizontal or descending ST-segment depression of at least 0.1 mV measured 80ms after the J-point in 3 consecutive cycles of at least two leads persisting for 6 minutes in the absence of chest pain / angina equivalent symptoms. If ST-depression was present on the resting ECG, an additional 0.1 mV depression was required. Electrocardiograms were recorded 6 min after exercise. Demographic information (age, gender, BMI, duration of diabetes) of the patients was also noted. All this information was recorded on a specially designed proforma.

The collected data was analysed statistically by using SPSS version 21. Quantitative variables like age, duration of diabetes and BMI were presented in the form of mean ± S.D. Qualitative variables like gender, smoking and silent myocardial ischemia were presented in form of frequency and percentage. Data was stratified for age, gender, BMI, smoking and duration of diabetes. Post-stratification, chi-square test was applied to compare frequency of silent myocardial ischemia in stratified groups. P-value $\leq$0.05 was considered significant.

RESULTS:

Mean age of the patients was 61.10±13.52 years, minimum and maximum age was 35 and 80 years. There were 69 (51.1%) male and 66 (48.9%) female patients. Mean body mass index was 30.09±5.70 kg/m^2. Mean duration of disease was 12.59±9.18 yesrs. Minimum and maximum duration of disease was 1 and 30 years. In this study 35(25.93%) patients were smokers. Overall, SMI was seen in 37(27.4%) patients. Patients in the age group 66-80 had significantly higher frequency of SMI (81.1%) as compared with patients in the age group 51-65 years of age (18.9%). i.e. p-value=0.000(Table-1.) No statistically significant difference was seen between two genders with respect to occurrence of SMI. (p-value=0.973). Obesity was significantly associated with SMI. Patients who had SMI, all of them were obese. i.e. p-value= 0.000 (Table-2.) Duration of disease was

Table-1: Comparison of SMI with age

Age	SMI present	SMI absent	p
35-50	0(0%)	31(31.6%)	0.000
51-65	7(18.9%)	37(37.8%)	
66-80	30(81.1%)	30(30.6)	
Total	37	98	

Table-2: Comparison of SMI with BMI

Body mass Index	SMI present	SMI absent	p
Normal	0(0%)	20(20.4%)	0.000
Overweight	0(0%)	32(32.7%)	
Obese	37(100%)	46(46.9%)	
Total	37	98	

Table-3: Comparison of SMI with duration of disease

Duration of DM (years)	SMI		p
	Yes	No	
1-5	0(0%)	49(50%)	0.000
6-10	1(2.7%)	10(10.2%)	
11-15	8(21.6%)	9(9.2%)	
16-20	16(43.2%)	10(10.2%)	
21-25	10(27%)	11(11.2%)	
26-30	2(5.4%)	9(9.2%)	
Total	37	98	

also significantly associated with SMI. Frequency of SMI increased with increase in duration of disease and vice versa; p-value=0.000 (Table-3). Smoking status of patients was not significantly associated with SMI. i.e. p-value= 0.535 Although it was observed that among non-smokers frequency of SMI was higher than that in smokers.

DISCUSSION

Silent Myocardial Ischemia is particularly of concern in diabetic patients. It is suspected that partial or complete autonomic denervation in diabetic patients causes impaired symptom perception e.g. lack of recognition of chest pain.[9] Microalbuminuria in type 2 DM reflects an underlying predisposition to developing progressive kidney diseases as well as serving as a marker of predilection for generalized cardiovascular disease.[10]

Persistent microalbuminuria has also been associated with an increased risk of atherosclerosis and cardiovascular mortality. Therefore, patients with diabetes should be screened regularly for microalbuminuria.[11] SMI leading to development of future CAD is common in Type 2 DM but more common in Type 2 DM with microalbuminuria. Therefore, microalbuminuria can be used as an early marker as well as for risk stratification of cardiovascular disease.[12]

In this study SMI was diagnosed in 27.4% of patients with type 2 diabetic patients with microalbuminuria. Age, BMI and duration of disease were significantly associated factors with SMI. Gender and smoking status of patients were not significantly associated with SMI.

Previous studies have demonstrated that SMI which is mainly caused by autonomic neuropathy occurring in about 20 to 25% of diabetic patients and the prevalence may be as high as 60% in those at high risk.[13] a study from Bangladesh reported that among type 2 diabetic patients with silent MI 42% patients were diagnosed with microalbuminuria. Odds ratio of 1.5 showed that MAU was a possible risk factor for SMI in type 2 DM.[4]

According to the results of a recently published study from India, there is statistically significant association between SMI and microalbuminuria. Prevalence of SMI was 60% among type 2 diabetic patients with microalbuminuria.[14] In our study, frequency of SMI was quite lower than that reported in the above mentioned Indian study. This difference may be due to the difference in sample size as in this study sample size was larger as compared to the above mentioned study.

Sonu Chauhan et al showed that besides microalbuminuria the factor which was predictive of SMI was male sex. When patients in the age group considered to be at risk for CAD were considered (males $\geq$ 45 years and females $\geq$ 55 years) a significant risk of SMI was found to be present in those belonging to the higher age group ($p = 0.05$). No other clinical variable like duration of diabetes, diabetic control, family history of premature CAD, smoking status, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), presence of central obesity or lipid profile were found to have a significant association with presence of SMI.[14] However age, BMI and duration of disease were significantly associated with SMI. These findings contradict the findings of above study wherein no statistically significant association was seen between these variables and SMI.

In this study, frequency of SMI was higher in male patients than in female patients but it was not statistically significantly. Although male Gender is considered a risk factor for CAD per se, but gender, in the present study, did not influence the incidence of SMI in patients with diabetes. This finding is supported by Sargin et al., who found no significant difference in the incidence of SMI between male and female diabetic patients. This may be, due to the loss of female protection from cardiovascular disease in the presence of diabetes mellitus.[15]

Walid m. Eltahawy et al showed that advanced age was associated with a higher incidence of inducible ischemia in their patients.[1] This is supported by several studies on patients with T2DM over the age of 65 years.1In this study same trend was seen that the frequency of SMI was highest in patients who were in the age group 66-80 years.

The concept that patients with diabetes have a higher prevalence of SMI than the general population was suggested by early clinical and autopsy studies and has since become accepted. Many recent large studies are available to confirm the high prevalence of silent ischaemia in diabetes but have been somewhat limited by the varying definitions of SMI between studies.

Why patients with diabetes have a higher prevalence of SMI than the general population? Several explanations are possible (including a different threshold of pain sensitivity or psychological denial) but cardiac autonomic neuropathy almost certainly plays an important role, potentially involving dysfunction at varying levels – from the pain receptors, afferent neurons or gating mechanisms to the supratentorial translation of ischaemia into pain. Many years ago, an autopsy study in a diabetic

patient who had silent infarction found pathologic changes in cardiac afferent neurons consistent with a neuropathy, and the prolonged anginal threshold reported in patients with DM has been found to occur in association with reduced heart rate variability, an early sign of cardiac autonomic nerve dysfunction[17]. The failure to develop angina at the onset of ischaemia will have a permissive effect on the diabetic subjects' exercise tolerance: they are able to exercise longer in the absence of chest pain and are at risk of developing more severe ischaemia as a result.[17]

Microalbuminuria is now recognised as a marker of endothelial dysfunction.[18] Endothelial dysfunction is considered to be one of the most important pathophysiological precursor to the development of cardiovascular disease. Thus the presence of microalbuminuria can be an important clue to identify asymptomatic diabetic patients with underlying cardiovascular disease. SMI can be suspected by the presence of MAU in type 2 DM. Therefore, MAU can be used particularly as a screening test for early detection of SMI. Early detection of SMI in type 2 DM can give the opportunity to treating physician to manage such patients more aggressively and possibly prevent future CAD. In conclusion, results of this study showed that SMI was seen in 27.4% patients. SMI was significantly associated with age, body mass index and duration of diabetes. Routine screening for SMI may be considered in T2DM with micralbuminuria.

Author's Contribution

ME:Wrote the article and collected the data.ZT: Conducted the study and collected the data.AS: Collected and re-arranged data.CMK & ZS: Corrections and did the proof reading.

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