ISSN 2515-8260 Volume 10, Issue 01, 2023

Silent Myocardial Ischemia in Type 2 Diabetic Patients Asymptomatic For Coronary Artery Disease : A Hospital Based Cross Sectional Study.

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Abstract:

Introduction: Diabetes mellitus type 2 usually occur in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. Various micro as well as macrovascular complications associated with chronic DM type 2.This study aimed to determine magnitude of one of the significant macrovascular complication i.e silent myocardial ischemia in selected asymptomatic DM outpatients by exercise tread mill test.

Material and Methods: This Cross sectional observational study was conducted at a tertiary care centre of Western India. Study population comprised of 125 asymptomatic type 2 Diabetes Mellitus patients, without any clinical evidence of Coronary Artery Disease, with normal resting ECG. Patients with Previous history of MI, heart failure, Evidence of angina pectoris, any additional chronic illness were excluded from the study. Silent Myocardial Infarction was identified using Treadmill test (TMT), conducted according to 'Bruce protocol' by CASE/T2100 sr number GE MAC.

Results: Proportion of Silent MI (Positive TMT) among Diabetics was 12.8%. TMT positivity was significantly associated with older age ($p=0.002$), duration of Diabetes for >10 years ($p<0.001$), dyslipidemia ($p<0.001$) and HbA1c >10% ($p<0.001$). Total cholesterol, LDL and Triglycerides were found to be significantly higher in TMT positive patients as compared to

ISSN 2515-8260 Volume 10, Issue 01, 2023

TMT negative patients. HDL level was significantly lower in TMT positive patients as compared to TMT negative patients.

Conclusion: A significant proportion of patients with type 2 Diabetes mellitus had silent myocardial infarction or asymptomatic Coronary artery disease. Diabetics with older age, obesity, dyslipidemia, high HbAIC had higher risk of silent MI. TMT could be used as a simple, non-invasive tool for early identification of Silent MI.

Key words: Silent ischaemia; asymptomatic Coronary artery disease; Exercise stress test; TMT; Diabetes

Introduction: Diabetes Mellitus (DM) is a metabolic disorder with hyperglycaemia . The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin leading to decrease glucose utilization and increase glucose production. According to W.H.O. India had 69.2 million people living with diabetes (8.7%) in 2015.[1]Diabetes has now become a global pandemic and unfortunately, the prevalence of diabetes is increasing most rapidly among developing countries of the world. In India within a span of 14 years(1989-2004), the prevalence of diabetes increased significantly by 72.3%.[2]

Diabetics may suffer from many acute and chronic complications. Acute complications are Diabetic ketoacidosis, Hyperosmolar hyperglycemic nonketotic coma and hypoglycemia. Chronic complications are classified into microvascular and macrovascular, microvascular complications are diabetes-specific viz Retinopathy, Neuropathy, Nephropathy. Macrovascular complications are Peripheral arterial disease [PAD], Coronary heart disease [CHD], Cerebrovascular disease similar to those in non diabetics but occur at greater frequency in individuals with diabetes.

Asymptomatic coronary disease observed with high frequency in type 2 DM. Traditional risk factors for CVD in T2D include hypertension, dyslipidemia, obesity, lack of physical activity, poor glycemic control, and smoking.[3,4] Patients with T2D have higher prevalence of lipid abnormalities.[4] Atherogenic dyslipidemia/diabetic dyslipidemia is a lipid disorder that is associated with insulin resistance.[4] Nontraditional risk factors for CVD in T2D include IR hyperinsulinemia, postprandial hyperglycemia, glucose variability, microalbuminuria, hematologic factors, thrombogenic factors, inflammation evidenced by elevated C-reactive protein, hyperhomocysteinemia and vitamin deficiencies, erectile dysfunction, genetics, and epigenetics.[5]

Diabetic patients mostly have been shown to have a higher incidence of silent ischemia than non diabetic patients.[6-8]There will be a reduced myocardial flow reserve in type 2 DM. Hyperglycaemia reduces availability of endothelium derived NO and affects vascular function mainly through the increased production of Reactive Oxygen Species. It has been hypothesized that key role in the sensation of angina played by afferent sympathetic fibers and in autonomic dysfunction these fibers may be disrupted.[8]

The ADA[9,10]advocates for stress testing in diabetic patients with (1) typical or atypical cardiac symptoms, (2) resting ECG suggestive of ischemia or infarction, (3) peripheral or carotid occlusive arterial disease, (4) sedentary lifestyle, age 35 years with plans to begin a vigorous exercise program, and (5) 2 or more of the following risk factors in addition to DM: total

cholesterol 240 mg/dL, LDL 160 mg/dL, HDL 35 mg/dL, blood pressure 140/90 mm Hg, smoking, family history of premature CAD, and microalbuminuria or macroalbuminuria.
Regular periodical clinical examination and resting electrocardiogram fail to detect coronary artery disease many times. Majority of patients can be identified by exercise electrocardiogram who likely to have significant ischemia during their daily activities and thus it remains the most important screening test for significant CAD.[11] Many studies attempted to elucidate the risk factors that can help to predict the subgroup of diabetics who are at risk for development of asymptomatic CAD but no consistent results have been found.[12] One such diagnostic tool is exercise treadmill test for the diagnosis and risk stratification of coronary heart disease whose diagnostic and prognostic value has been studied extensively.[13] For diabetes management, exercise is considered to be a cornerstone, concurrently with diet and medication.[14] Diabetic patients are usually advised to engage in either indoor or outdoor exercises and encourage utilization of fitness equipment such as treadmill as it are same as walking.
There are presently no evidence-based guidelines available for screening asymptomatic diabetic patients for coronary artery disease (CAD) significantly. One well-studied screening tool is exercise treadmill testing. Many diabetic patients with no symptoms of CAD have abnormal stress tests. For asymptomatic patients, identification of cardiovascular risk factors and risk stratification may help physicians justify the performance of treadmill evaluation. This present study was aimed to determine magnitude of silent myocardial ischemia in selected asymptomatic DM outpatients by exercise tread mill test and for investigating the utility of treadmill test in type II DM patients.

Material and Methods: This Cross sectional observational study was conducted in department of General Medicine, at a tertiary care centre of Rajasthan. Study population comprised of asymptomatic type 2 Diabetes Mellitus patients, aged 40-60 yrs of age, of either gender, without any clinical evidence of Coronary Artery Disease, with normal resting ECG attending, Diabetology or medicine OPD. Sample size was calculated at 95% confidence interval and 10% allowable error, expected 37% proportion of TMT positivity among asymptomatic diabetic patients. Sample size was calculated using the formula for sample size for estimation of a single sample proportion –

$$N = \frac{{Z_{1-\alpha/2}}^2 \; P\,(1-P)}{E^2}$$

Sample size was calculated to be a minimum of 94 subjects, considering 10% non response rate sample size was enhanced and round to 125 subjects. Patients with Previous history of MI, heart failure, Evidence of angina pectoris, Anaemia, Hypertension, Renal disease, ECG evidence of Q wave MI, ischemic ST–segment or T wave abnormality or completed LBBB, any chronic illness because of cancer and ESRD or liver disease were excluded from the study. Ethical clearance was obtained from Institutional Ethics Committee prior to initiation of study. Written informed consent was obtained from all patients prior to data collection.

Each patient was subjected to detailed history taking, general and specific clinical examination, resting ECG & all relevant investigations (CBC, RFT, HB1AC, FBS, LIPID PROFILE, COMPLETE URINE EXAMINATION) to decide for eligibility. All the blood

sampling and testing was performed at the central laboratory of the centre using similar standard protocol. Patient were asked to report in hospital clinics next day morning after overnight 4-5 hours of non caloric intake for treadmill test. Smoker and alcoholic were instructed to abstain from smoking and alcohol on the morning of investigation. The cases were said to have normal BMI when it ranged Between 18.5 – 22.9 kg/m2 Overweight when BMI ranged between 23 – 24.9 kg/m2 And obese when BMI was 25 -29.9 kg/m^2 .Abdominal obesity was defined was waist circumference of more than 90 cm in men and 80 cm in women as per the modified NCEP ATP III guidelines for Asian population.[15]Treadmill test was done conducted in all study subjects using a standard protocol under similar conditions. It was done according to 'Bruce protocol' by CASE/T2100 sr number GE MAC. The maximum heart rate targeted was '220 - age of patient'. If patient got chest pain or shortness of breathing the procedure was stopped.

Statistical analysis: Categorical variables were expressed as frequency and percent and were analyzed using Chi square test. Continuous variables were expressed as mean and Standard Deviation and analyzed using independent sample t-test. A p value <0.05 was taken as statistically significant. All statistical analysis was done using EPI INFO™ version 7.2.1.0, CDC, Atlanta, GA, USA, 2017 statistical software.

Results:

Mean age of diabetic patients in present study was 48.89 ± 6.1 years with a male : female ratio of 1.72 : 1. Incidence of Silent MI (Positive TMT) among Diabetics was found to be 12.8% (Figure 1). Silent MI (TMT positivity) was seen significantly (p=0.002) more in subjects aged 50 – 60 years (21.4%) as compared to those aged 40 – 50 years (5.8%). TMT positivity was seen more in subjects with Diabetes for >10 years (55.6%) as compared to those with diabetes 5- 9 years (6.7%) and DM<5 years (4.3%). TMT positivity was significantly higher in subjects with dyslipidemia (50%) as compared to subjects without dyslipidemia (4%). TMT positivity was higher in subjects with HbA1c >10% (60%) as compared to subjects with HbA1c 7 – 10% (10.1%), and HbA1c <7% (Table 1). Proportion of silent MI was more in subjects with high BMI, high Waist circumference, smokers, ancoholic and physically inactive subjects (Table 1). Total cholesterol, LDL and Triglycerides were found to be significantly higher in TMT positive patients as compared to TMT negative patients. HDL level was significantly lower in TMT positive patients as compared to TMT negative patients. Mean HbA1c was significantly higher in TMT positive subjects (10.19%) as compared to TMT negative subjects (7.74%).

ISSN 2515-8260 Volume 10, Issue 01, 2023

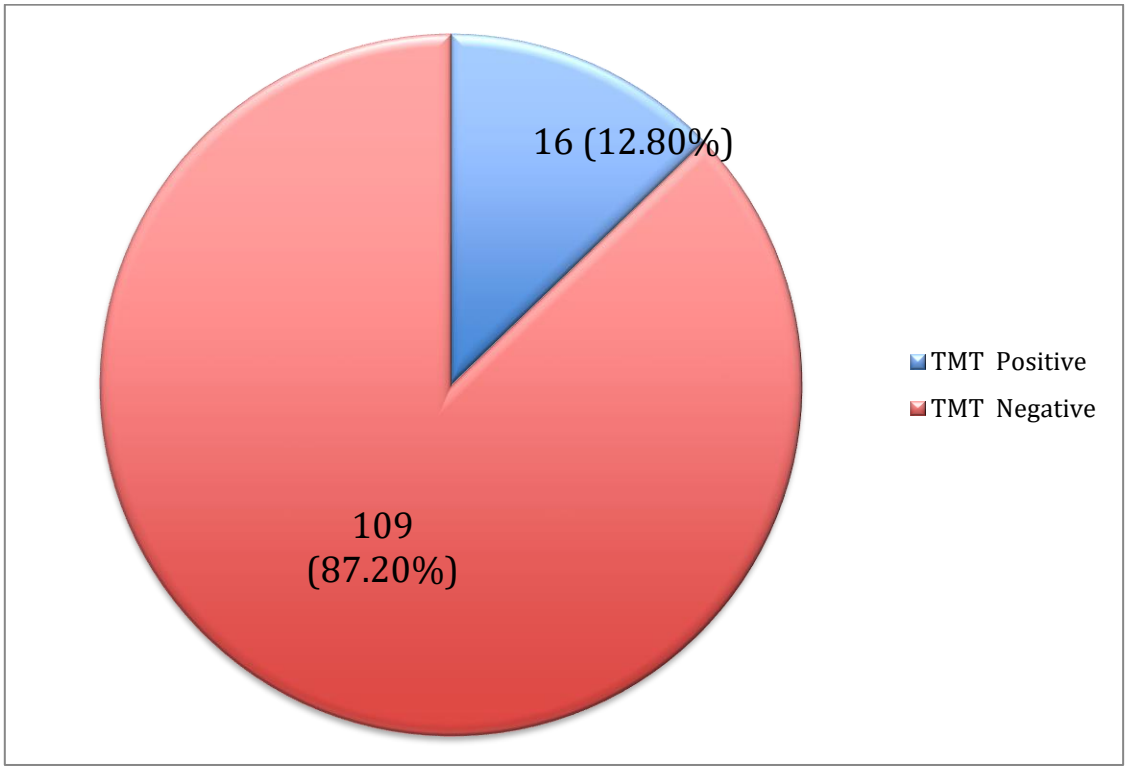

Figure 1: Distribution of study subjects according to TMT findings

Table 1: Factors associated with silent MI among diabetic patients

Variables		TMT Negative		TMT positive		Total	P value
		N	%	N	%	N	
Age group	40 -50 years	65	94.2	4	5.8	69	0.002 (S)
	50-60 years	44	78.6	12	21.4	56	
Gender	Female	47	85.5	8	14.5	55	0.084
	Male	62	88.6	8	11.4	70	
Socio-economic status	Lower	23	92	2	8	25	
	Middle	80	85.1	14	14.9	94	
	Upper	6	100	0	0	6	0.414
Residence	Rural	65	89.0	8	11.0	73	
	Urban	44	84.6	8	15.4	52	0.647
Duration of diabetes (years)	<5 years	45	95.7	2	4.3	47	
	5-9 years	56	93.3	4	6.7	60	<0.001 (S)
	10-15 years	8	44.4	10	55.6	18	
BMI (Kg/m^2)	18.5 – 22.9 Kg/m^2	27	93.1	2	6.9	29	
	23 – 24.9 Kg/m^2	35	85.4	6	14.6	41	
	≥25 Kg/m^2	47	85.5	8	14.5	55	0.555
Waist circumference	Normal WC	23	92	2	8	25	
	Raised WC	86	86	14	14	100	0.639

Smoking history	**Smoker**	20	76.9	6	23.1	26	0.152
	Non smoker	89	89.9	10	10.1	99	
Alcoholic habit	**Alcoholic**	19	76	6	24	25	0.124
	Non alcoholic	90	90	10	10	100	
physical activity	**Active**	81	89.0	10	11.0	91	0.490
	Inactive	28	82.4	6	17.6	34	
Dyslipidemia	**Present**	12	50	12	50	24	<0.001 (S)
	Absent	97	96.0	4	4	101	
HbA1c (%)	**< 7%**	34	94.4	2	5.6	36	<0.001 (S)
	7 – 10%	71	89.9	8	10.1	79	
	> 10%	4	40.0	6	60.0	10	

Table 2: Laboratory parameters in relation to TMT results

	TMT positive	**TMT negative**	**P value**
TC (mg/dl)	385 ± 137.4	273.6 ± 74.63	0.026 (S)
LDL (mg/dl)	149.2 ± 69.55	124.6 ± 35.5	0.027 (S)
HDL (mg/dl)	29.69 ± 11.52	38.27 ± 10.88	0.004 (S)
TG (mg/dl)	235.8 ± 140.5	149.1 ± 46.95	<0.001 (S)
FBS (mg/dl)	165.2 ± 81.53	144.7 ± 73.92	0.308
HbA1c (%)	10.19 ± 2.92	7.74 ± 1.32	<0.001 (S)
Blood urea	31.38 ± 11.41	32.2 ± 10.11	0.764
Serum creatinine	0.93 ± 0.22	0.85 ± 0.23	0.182

Discussion: The present study was aimed at asymptomatic presentation of coronary artery disease among diabetic patients with normal resting ECG ,with looking at TMT positivity. The study involved 125 diabetic mellitus patient with normal resting electrocardiographic evidences, testing done with Tread mill test. Mean age of the patients in present study was found to be 48.89 ± 6.1 years, majority of diabetic subjects were in age group of 45 – 49 years. Similarly **Dipankar Deb et al [16]** observed that majority of patients were in the age group 35-44 years. **Amit Daphale et al [17]** found the mean age to be 46.20±12.20 years. Majority of study subjects were males, which is in conformance with other studies by **CJ Ditchburn et al [18],Dipankar Deb et al [16]**and **Anil Shrinivasrao Joshi et al [19].**

Most of the diabetic patients were found to have chronic diabetes for 5-9 years similar to what observed by **Dr K Swaminathan and Dr M Gayathri (2016)[20].** Tread mill test results in asymptomatic diabetic patients revealed that 12.8% were TMT positive and thus have silent MI. Similarly **M J Koistinen[21]**found that asymptomatic coronary artery disease with active myocardial ischaemia in the diabetic population was present among 9% . **Langer A et al[22]**found that 17% asymptomatics were having MI. However many of the studies found the

figure to be on higher side like **Anurag S Lavekar (2013)[23]** observed that 21.1% were found positive for exercise induced ischemia. **Dipankar Deb et al (2016)[16]** observed that TMT result was positive in 27 patients (27%). Slight higher than that, **Sharda M et al (2016)[24]** found prevalence of 37.3% of Silent MI in DM-2 patients. **Dr K Swaminathan and Dr M Gayathri (2016)[20]** observed TMT positivity in 30 % of patients. Certain studies observed prevalence to be more than 50% like **Marin Huerta E et al (1989)[25]** found 58 % diabetics to be at risk of silent MI, **Motoji N (1991)[26]** revealed that 31% of diabetics were TMT positive, **CJ Ditchburn et al (2001)et al[18]** found that sixty six of the diabetic patients had positive exercise tests and silent ischaemia was detected in 34 patients, **A K Agarwal et al (2008) [12]**observed that 28.9% diabetics were found to have silent CAD as evidenced by a positive TMT result.

Looking at the factors associated with TMT positivity ,present study found that elderly patients with age more than 50 years significantly observed more TMT positivity in present study.Similar findings observed by **PK Garg et al (2002)[27], A K Agarwal et al (2008)[12], Won sang yoo et al (2009)[28], Anurag S Lavekar (2013)[23], Sharda M et al (2016)[24] and**. **Dr K Swaminathan and Dr M Gayathri (2016)[20].** TMT positivity was seen slightly more in females (14.5%) as compared to males (11.4%) in present study . TMT positivity was seen more in middle SES patients (14.9%) as compared to those in Lower SES (8%) however those were not found to be statistically significant.

In the present study TMT positivity was seen more in subjects with Diabetes for >10 years (55.6%) as compared to those with diabetes 5- 9 years (6.7%) and DM<5 years (4.3%) and that finding was observed to be statistically significant. Similar findings observed by **A K Agarwal et al (2008)[12], Won sang yoo et al (2009)[28] ,Anurag S Lavekar (2013)[23] Dipankar Deb et al (2016)[16],**and **Sharda M et al (2016)[24]**. **Dr K Swaminathan and Dr M Gayathri (2016)[20] and Anil Shrinivasrao Joshi et al(2017)[19]** in separate studies also found that majority of patients with TMT positivity were having duration of diabetes more than 10 years.

TMT positivity was seen higher in subjects with BMI ≥ 25 Kg/m^2 (14.5%) and BMI 23. – 24.9 Kg/m^2 (14.6%) as compared to those aged with BMI <23 Kg/m^2 (6.9%) in present study TMT positivity was higher in subjects with raised WC (14%) however those differences were not found to be statistically significant.

TMT positivity was seen higher in subjects with dyslipidemia (50%) and this difference in TMT positivity in relation to dyslipidemia was found to be statistically significant. Total cholesterol, LDL and Triglycerides were found to be significantly higher in TMT positive patients .Similarly, HDL level was also found to significantly lower in TMT positive patients as compared to TMT negative patients. Similar findings were observed by **R C Turner et al (1998)[29], Anurag S Lavekar (2013)[23], Anil Shrinivasrao Joshi et al(2017)[19].**

Mean HbA1c was higher in TMT positive subjects (10.19%) as compared to TMT negative subjects (7.74%). This difference in mean HbA1c was found to be statistically significant. TMT positivity was higher in subjects with HbA1c >10% (60%) as compared to subjects with HbA1c 7 – 10% (10.1%), and HbA1c <7% (5.6%) and this difference in TMT positivity in relation to HbA1c was found to be statistically significant. Similar findings observed by **R C Turner et al (1998)[29], Anurag S Lavekar (2013)[23], Dr K Swaminathan and Dr M Gayathri (2016)[20].**

Conclusion:
A significant proportion of patients with type 2 Diabetes mellitus had silent myocardial infarction or asymptomatic Coronary artery disease. Diabetics with older age, high BMI, abdominal obesity, dyslipidemia, uncontrolled blood sugar, smoker and alcoholics had higher risk of silent MI. Exercise stress test or TMT could be used as a simple, non-invasive and cost effective tool for early identification of Silent MI or asymptomatic CAD. Also identification of the associated factors allow for early screening of these patients in particular to avert any impending cardio vascular event.

CONSENT
As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL
As per international standard guideline written ethical approval has been collected and preserved by the author(s).

COMPETING INTEREST
Authors have declared that no competing interests exist.

FUNDING
No funding sources

Acknowledge: We acknowledge the Central laboratory staff, and TMT technicians for their contribution.

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