ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

ORIGINAL RESEARCH

Study of exercise induced ischemia in newly diagnosed asymptomatic diabetic patients

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Abstract
Aim: To analyse exercise induced ischemia in newly diagnosed asymptomatic diabetic patients.
Material and Methodology: This prospective observational study was conducted in the department of medicine from November 2021 to August 2022. Informed consent of all participants was obtained after explaining the purpose of the study. Permission to carry out the study was obtained from the Institutional Ethical Committee. 100 patients of newly diagnosed asymptomatic type 2 diabetes without clinical evidence of coronary artery disease attending Medicine OPD were recruited for the present study. During the exercise test, data about heart rate, blood pressure and ECG changes was obtained at the end of each stage and at any time an abnormality is detected with cardiac monitoring. Angina or significant ST depression (greater than 2 mm) before completing Stage 2 of the Bruce protocol and/or ST depressions that persist for more than 5 minutes into recovery suggest severe ischemia and high risk for coronary events.
Results: Only 2% of the subjects had positive TMT. Mean FBS (mg/dl) and PPBS (mg/dl) was found to be higher among TMT positive as compared to TMT negative subjects, though no significant difference was found. Mean HbA1c (%) was 10.02±1.38 and 8.05±1.14 among the TMT positive and negative subjects respectively with statistically significant difference as $p<0.05$.
Conclusion: We concluded that duration of diabetes, triglycerides level, HbA1c level are strong clinical predictors for SMI in patients of Type 2 DM asymptomatic for exercise induced ischemia.
Keywords: Ischemia, Type 2 Diabetes, HbA1c, ECG

Introduction

Diabetes mellitus (DM) is a leading cause of cardiovascular mortality[1]. Coronary artery disease (CAD) is the leading cause of death in patients with type 2 diabetes mellitus (Type 2 DM) and is often asymptomatic because of silent myocardial ischemia (SMI). The prevalence of CAD in our country has increased, making it a major cause of morbidity and mortality[2]. According to the International Diabetes Federation, India has over 61.3 million diabetic patients which had increased from 50.8 million last year[3]. Data from Framingham heart study demonstrates the increased and poor prognosis of cardiovascular disease (CVD) in DM. Mortality related to CVD is doubled in diabetic men and quadrupled in diabetic women over that in their non-diabetic counter parts[4].

It was also observed in majority of patients under high risk for Ischemic Heart Disease that they were unaware of their health condition. Even with complaints of chest pain, breathlessness and uneasiness, the patients were careless about their health. From epidemiological perspective, a "risk factor" is a feature of individual or population that is present early in the life and is associated with increased risk of developing disease in the future. Risk factors of interest for ischemic heart disease may be hypertension, diabetes mellitus, smoking, hyperlipidemia, obesity, and physical inactivity[5].

During extensive work in the field of ischemic heart, it was accidentally noted that ST segment changes occur in the Electrocardiogram leads during exercise in the patients with a history of angina[6].

The methods for screening asymptomatic CAD in diabetics may vary and are not unified. While coronary angiography is the gold standard for identifying CAD, this invasive technique is reserved for patients with evidence of ischemia on a stress test or for those with continuous cardiac symptoms. Therefore several non-invasive tools have been recommended for primary screening of asymptomatic CAD in diabetics, including exercise stress testing (EST), single-photon emission computed tomography (SPECT), multidetector computed tomography (MDCT), coronary computed tomography angiogram (CCTA), and stress echocardiography.[7]

Among those approaches, EST is the most common tool applied to individuals with suspected CAD. Compared with alternative methods, EST is non-invasive, cost-effective, free from radiation, and widely available, affirming its

ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

appropriateness as an initial screening tool. In addition, it also has prognostic value by providing information on exercise capacity, dysrhythmia evaluation, heart rate response and hemodynamic response.[7]

To date, there is no higher level clinical evidence to probe into the diagnostic value of EST in asymptomatic patients with T2DM[10]. Hence the present study was conducted to analyse exercise induced ischemia in newly diagnosed asymptomatic diabetic patients.

Material and Methodology

This prospective observational study was conducted in the department of medicine from November 2021 to August 2022. Informed consent of all participants was obtained after explaining the purpose of the study. Permission to carry out the study was obtained from the Institutional Ethical Committee. 100 patients of newly diagnosed asymptomatic type 2 diabetes without clinical evidence of coronary artery disease attending Medicine OPD were recruited for the present study.

Inclusion Criteria

1. All type 2 newly diagnosed asymptomatic diabetic patients without anydiabetic complications
2. Patients that gave informed consent for treadmill testing
3. Patients with normal resting ECG

Exclusion Criteria

1. Previous history of myocardial infarction, heart failure
2. History of Angina pectoris
3. Abnormal coronary angiography
4. Hypertension
5. End stage Renal Disease or serum creatinine > 3mg/dl
6. All the patients with bone diseases.
7. Limited life expectancy due to cancer and end stage renal or liver disease.
8. History of coronary revascularization
9. Symptomatic peripheral vascular disease
10. Severe vascular disease or any known cardiomyopathy Equipment

Treadmills are much more commonly used for exercise testing. Although much of the published data are based on the Bruce protocol, there are clear advantages to customizing the protocol to the individual patient to allow 6 to 12 minutes of exercise.

Technique

During the exercise test, data about heart rate, blood pressure and ECG changes was obtained at the end of each stage and at any time an abnormality is detected with cardiac monitoring. In general, heart rate and systolic blood pressure rise with each stage of exercise until a peak is achieved. The baseline ECG was evaluated closely prior to starting the exercise portion of the test. Once it was determined that there are no limiting factors based on baseline ECG, the patient is placed on a treadmill with a designed protocol that increases in intervals as you exercise. Blood pressure and heart rate are monitored throughout exercise, and the patient is monitored for any developing symptoms such as chest pain, shortness of breath, dizziness or extreme fatigue.

Protocols for Treadmill Test

The most common protocol used during treadmill exercise stress testing is the Bruce protocol. This protocol was divided into successive 3-minute stages, each of which requires the patient to walk faster and at a steeper grade. The testing protocol was adjusted to a patient's tolerance, aiming for 6 to 12 minutes of exercise duration. Patients were questioned about any symptoms they experience during exercise. All patients were monitored closely during the recovery period until heart rate, and ECG are back to baseline, as arrhythmias and ECG changes can still develop.

Normal test is when patient's blood pressure and heart rate increase appropriately to graded exercise. There should be no ECG changes suggestive of ischemia and no arrhythmias during testing. Failure of the blood pressure to increase or a decrease with signs of ischemia has a significant prognostic indication. Angina or significant ST depression (greater than 2 mm) before completing Stage 2 of the Bruce protocol and/or ST depressions that persist for more than 5 minutes into recovery suggest severe ischemia and high risk for coronary events.

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p < 0.05$.

ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

Results

Males (63%) were comparatively more as compared to females (37%). Maximum subjects were from the age group of 41-50 years (67%) while minimum subjects were from the age group of 31-40 years (6%).

Gender	N	%
Male	63	63
Female	37	37
Age Group (in years)		
31-40	6	6
41-50	67	67
51-60	11	11
>60	16	16
Total	100	100

Table 1: Gender and age distribution among the study subjects

The mean SBP and DBP among the study subjects was 127.42±11.83 and 75.16±7.21 mmhg respectively. Hence SBP and DBP was found to be in normal range (table 2).

Blood Pressure (mmhg)	Mean	SD
BMI (kg/m^2)	24.71	3.42
SBP (mmhg)	127.42	11.83
DBP (mmhg)	75.16	7.21

Table 2: Blood pressure among the study subjects

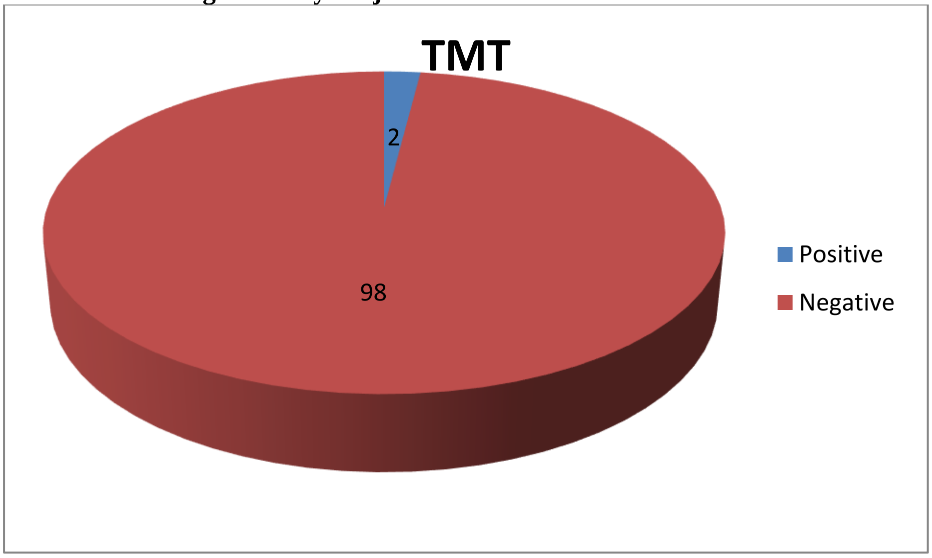
All the diabetic parameters viz. FBS (mg/dl), PPBS (mg/dl) and HbA1c (%) were found to be in higher range i.e. mean FBS (mg/dl), PPBS (mg/dl) and HbA1c (%) was 181.74±33.80, 229.35±57.92 and 8.63±1.22 respectively. Mean cholesterol (mg/dl), TG (mg/dl), LDL (mg/dl) and HDL (mg/dl) among the study subjects was 177.02±26.85, 126.31±29.62, 116.96±29 and 33.8±1.27 respectively (table 3).

Variables	Mean	SD
FBS (mg/dl)	181.74	33.80
PPBS (mg/dl)	229.35	57.92
HbA1c (%)	8.63	1.22
Cholesterol (mg/dl)	177.02	26.85
TG (mg/dl)	126.31	29.62
LDL (mg/dl)	116.96	29
HDL (mg/dl)	33.8	1.27

Table 3: Diabetic and lipid profile among the study subjects

Negative TMT was found among 2% of the study subjects. Only 2% of the subjects had positive TMT (graph 1).

Graph 1: TMT outcomes among the study subjects



ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

Mean age among TMT positive and negative was found to be 49.98±7.02 and 48.13±5.19 respectively. When mean age was compared according to TMT outcome, insignificant difference was found as p>0.05. Mean BMI and blood pressure was found to be comparable among the subjects with TMT positive and negative outcome as p>0.05 (table 4).

Variables	TMT				t test	p value
	Positive		Negative			
	Mean	SD	Mean	SD		
BMI (kg/m^2)	24.97	3.35	24.64	3.49	0.92	0.71
SBP	129.05	10.23	126.11	12.07	1.06	0.48
DBP	76.09	6.80	74.98	8.12	0.97	0.63

Table 4: Mean BMI and blood pressure among the study subjects according to gender

Mean FBS (mg/dl) and PPBS (mg/dl) was found to be higher among TMT positive as compared to TMT negative subjects, though no significant difference was found. Mean HbA1c (%) was 10.02±1.38 and 8.05±1.14 among the TMT positive and negative subjects respectively. When HbA1c (%) was compared according to TMT outcome, significant difference was found as p<0.05 (table 5).

Variables	TMT				t test	p value
	Positive		Negative			
	Mean	SD	Mean	SD		
FBS (mg/dl)	189.33	31.66	177.45	34.67	1.68	0.22
PPBS (mg/dl)	234.07	51.42	226.09	58.74	1.38	0.35
HbA1c (%)	10.02	1.38	8.05	1.14	7.54	<0.01*

Table 5: Mean diabetic profile among the study subjects according to gender

*: statistically significant

Discussion

Involvement of the cardiovascular system in diabetes is a spectrum of ischaemic heart disease (IHD), diabetic cardiomyopathy, cardiac autonomic neuropathy and preclinical heart disease[8]. Silent myocardial ischaemia (SMI) has been reported to occur more frequently in diabetic patients, according to some studies[9].

There are multiple means by which SMI can be documented, but the treadmill test (TMT) with the stress electrocardiography test and ambulatory ECG monitoring (Holter monitoring) are the most important and useful methods[10-12].

Males (63%) were comparatively more as compared to females (37%) in this study. According to Pawan Kumar Goyal[13], the ratio of female to male was 1:1.5. Lovleen C. Bhatia et al[14] in their study revealed similar male dominance.

Maximum subjects were from the age group of 41-50 years (67%) while minimum subjects were from the age group of 31-40 years (6%). Lovleen C. Bhatia et al[14] in study too found maximum subjects in the age group of 41-50 years. In a study by Pawan Kumar Goyal[13], the mean age was 48.75 ± 7.46 years with range of 34-60 years.

Negative TMT was found among 2% of the study subjects in this study. Pawan Kumar Goyal[13] in their study showed that out of 102 patients, TMT was found positive in 23 patients. It was positive in 12% among diabetic patients. Achari and Thakur[15] reported a 42.5% incidence of ischaemia in patients with asymptomatic type 2 diabetes. Ahluwalia et al[16] reported the incidence of SMI in asymptomatic diabetic patients to be 50% on an exercise ECG and 35% on an ambulatory ECG compared with 10% and 5% in nondiabetic subjects by these two methods, respectively. Seshiah et al[17] reported 60% stress test positivity in diabetic patients in his study. Finally, Zharov et al[18] also found that 42.5% of diabetic patients had a positive stress test.

Lovleen C. Bhatia et al[14] in their study reported significant relationship between a positive TMT and age in diabetic patients and controls. They revealed incidence of positive stress test of 50% in asymptomatic diabetic subjects compared with 23% in asymptomatic control subjects, which is very high in comparison to our study. These differences in incidence might be due to the difference in study area and study population as well as methodology.

Only 2% of the subjects had positive TMT. TMT was found to be positive only in male subjects. When TMT outcome was compared statistically among male and female using chi square test, no significant difference was found. Mean age among TMT positive and negative was found to be 49.98±7.02 and 48.13±5.19 respectively. When mean age was compared according to TMT outcome, insignificant difference was found as p>0.05. Mean BMI and blood pressure was found to be comparable among the subjects with TMT positive and negative outcome as p>0.05. Mean FBS (mg/dl) and PPBS (mg/dl) was found to be higher among TMT positive as compared to TMT negative subjects, though no significant difference was found. Mean HbA1c (%) was 10.02±1.38 and 8.05±1.14 among the TMT positive and negative subjects respectively. When HbA1c (%) was compared according to TMT outcome, significant difference was found as p<0.05 in this study.

Lovleen C. Bhatia et al[14] in their study found that the incidence of positive stress test was higher in older (48%) compared with younger (2%) diabetic patients. A similar trend was observed in the control group (23.3% vs 0%), thus suggesting the potential contribution of aging in the pathogenesis of CAD along with diabetes. Stress test positivity increases with aging in both diabetic and non-diabetic patients[19]. Similarly Pawan Kumar Goyal[13] in their study found that there was a significant correlation between TMT negative and TMT positive patients with reference to HbA1c ($p<0.001$). De Luca et al[20] found that among 54 patients who had diabetes, SMI was present in 27 patients (50%) who had HbA1c ≥ 7.6% ($p<0.005$). Hence, it is concluded that the increased levels of HbA1c indicates poor glycemic control and has a great influence on CAD.

Mean cholesterol (mg/dl), TG (mg/dl), LDL (mg/dl) and HDL (mg/dl) among the study subjects was 177.02±26.85, 126.31±29.62, 116.96±29 and 33.8±1.27 respectively. Hence dyslipidaemia was one of the important risk factor in this study. This correlates well with the fact that diabetic patients have hypertriglyceridaemia. LDL is usually normal but this is small, dense LDL, which is more atherogenic. It is a well known fact that dyslipidaemia is present in diabetic patients and that it is a major risk factor for CAD. It was also found that dyslipidaemia was significantly higher in diabetic patients who were positive responders. Similar observations were made in other studies[15,17,18].

According to Lovleen C. Bhatia et al[14], the prevalence of dyslipidaemia was significantly higher in the diabetic group compared with the control group (56% in diabetic patients and 16.6%in controls) [$p < 0.05$]. There was no significant difference for high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels between the diabetic and control groups; however, it was found that diabetic patients had significantly higher levels of total cholesterol (191.01±37.73 vs 165.63±25.83mg/dL; $p < 0.05$) and serum triglycerides (160.96±108.68 vs 118±31.94 mg/dL; $p < 0.05$).

Another similar study by Scheidt-Nave et al[21] showed higher prevalence of SMI in diabetics as compared to non-diabetics. In the study, 31% diabetics without prior evidence of CAD had TMT positive and SMI was 2.2 times more in diabetics as compared with non-diabetics. Similarly Pawan Kumar Goyal[13] in their study found that there was a significant correlation between TMT negative and TMT positive patients with reference to triglycerides (TG) level ($p=0.001$).

The limitation of the present study is small sample size.

Conclusion

We concluded in the study that only HbA1c (%) was significantly associated with positive TMT. Longer the duration of diabetes, greater the risk of SMI. Dyslipidemia (mainly raised TGs) is found to be more in diabetics and is directly related to higher prevalence of SMI in them. HbA1c levels are found to be more in diabetics with poor glycemic control and had greater influence on CAD. Hence, it is concluded from the study that duration of diabetes, triglycerides level, HbA1c level are strong clinical predictors for SMI in patients of Type 2 DM asymptomatic for exercise induced ischemia.

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ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

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