Original Research Article

Silent myocardial ischemia in patients with type 2 diabetes mellitus by a treadmill test

Abdulmuthalif Mohamedkalifa[1], Archana Gaur T[2], Jeganathan Geetha[3], Nachimuthu Maithilikarpagaselvi[4], Varatharajan Sakthivadivel[5*]

[1]Associate Professor, Department of General Medicine, Government Kilpauk Medical College, Chennai, Tamilnadu, India

[2]Assistant Professor, Department of Physiology, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India

[3]Senior Resident, Department of General Medicine, Karpaga Vinayaga Institute of Medical Sciences and Research Center, Maduranthgam, Tamilnadu, India

[4]Assistant Professor, Department of Biochemistry, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

[5]Associate Professor, Department of General Medicine, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India

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Abstract

Background: Silent myocardial ischemia (SMI) is common in patients with diabetes mellitus. Coronary artery disease-related mortality is the leading cause in patients with diabetes mellitus. This can be prevented by early detection and intervention. The treadmill test is the commonly used modality to detect silent myocardial ischemia. **Aim:** Our study aimed at detecting silent myocardial ischemia in patients with type 2 diabetes mellitus by a treadmill test. **Materials and methods:** Out of 205 patients enrolled in the study, 40 patients with type 2 diabetes mellitus were selected as cases as per selection criteria and 20 healthy volunteers were selected as controls. Baseline characters and risk factors were noted. Biochemical parameters were measured. A treadmill test (TMT) was done. Two patients were excluded because of inconclusive TMT results. **Results:** Prevalence of silent myocardial ischemia was 26.3%. A significant difference was noted between cases and controls in FBS, PPBS, HbA1C, HDL cholesterol, family history of diabetes mellitus, TMT exercise time, workload, and percentage of targeted heart rate. A significant difference was noted between TMT positive and negative patients in view of age, hypertension, smoking, duration of diabetes mellitus, TMT exercise time, and workload. **Conclusion:** Silent myocardial ischemia is common in patients with diabetes mellitus with Male predilection.

Key words: Silent myocardial ischemia, Type 2 diabetes mellitus, Treadmill test

Introduction

Diabetes mellitus is a global health concern given its strong predisposition to atherosclerosis. Diabetes mellitus climbed to the eighth position as the cause of disability-adjusted life years in 2016. The predicted prevalence of diabetes in adults is 10.9% (700 million) in 2045 [1]. Coronary artery disease is more frequent and extensive in patients with diabetes. The prevalence of coronary heart disease in patients with diabetes is nearly 21% as per recent systematic literature review [2]. Cardiovascular disease is the major cause of death in diabetes mellitus with a death rate of 15.4% without myocardial infarction and 42% with prior myocardial infarction [3]. Myocardial infarction is more extensive and recurrent in patients with diabetes mellitus. Patients with diabetes mellitus are more prone to silent ischemia. Silent myocardial ischemia (SMI) is defined by the objective evidence of myocardial ischemia without angina or equivalent symptoms.

*Correspondence

Dr. Varatharajan Sakthivadivel

Associate Professor, Department of General Medicine, AIIMS, Bibinagar, Hyderabad, Telangana, India

E-mail: vsakthivadivel28@gmail.com

SMI is diagnosed by a positive Exercise test in an asymptomatic individuals, random (or) ambulatory electrocardiography abnormality, rest or stress-induced echocardiography abnormality, and myocardial perfusion imaging [4].

Treadmill test(TMT) is the most frequently used methodology to diagnose SMI. The sensitivity and specificity of TMT are 68% and 77% respectively. Females have high false positiveTMT [5].TMT predictive value may be increased by analyzing exercise time, workload, heart rate, and BP response [6]. Screening for cardiovascular risk in patients with type 2 diabetes mellitus (T2DM) is vital to prevent cardiovascular morbidity and mortality. Hence this study was conceived to estimate the prevalence of silent ischemia in patients with T2DM by using a treadmill test.

Materials and Methods

Study Population

This case-control study was conducted after obtaining institutional ethical committee approval in the department of General Medicine in collaboration with the department of cardiology at a tertiary care institute in Northern Tamilnadu, India. Patients with T2DM between 30 to 60 years of age without anginal symptoms and with normal electrogram, echocardiogram, and chest skiagram were included in this study. Patients with type 1 diabetes mellitus, known coronary artery disease, peripheral arterial disease, uncontrolled hypertension, arrhythmia, and uncooperative patients were excluded from the study.

Out of the 205 patients enrolled, 40 Patients of T2DM were selected for the treadmill test as per selection criteria. Twenty healthy non-diabetic volunteers were selected as control. TMT was performed using standard Bruce protocol [7].

Laboratory Methods

Fasting plasma glucose (FBS) and postprandial glucose (PPBS) were measured after 8 hours of fasting and 2 hours after routine breakfast by semi autoanalyzer using glucose oxidase and pyruvate oxidase method. After 12 hours of overnight fasting, Lipid profile (Serum total cholesterol, HDL, TGL) was measured by ERBA KIT semi autoanalyzer using the enzymatic method. Serum LDL was calculated using Friedwald's formula [8]. HbA1C was measured by the HPLC method. Body mass index **(**BMI) was calculated by using the formula: BMI = Weight in Kg / (Height in meters)^2 [9].

Tread Mill Test

Initially written informed consent was obtained. Patients were instructed to wear loose clothes and comfortable shoes and advised not to eat or drink caffeine products for 3 hours before testing. Room temperature was maintained between 18-22°C. Electrode application areas were rubbed with alcohol to reduce skin resistance. The heart rate, blood pressure and ECG were recorded at the end of each stage of the exercise, at the onset of an ischemic response, and for each minute for at least 5-10 minutes in the recovery phase. Patients were advised to maintain sitting posture after the procedure. Total exercise duration was noted. Onset of chest pain, dyspnoea, fatigue, hypertension, hypotension, arrhythmia and down sloping ST depression >1mm or ST elevation were the indications of termination of the test.

Normal response: PR, QRS, and QT intervals shorten due to tachycardia. The amplitude of P increases and down sloping of PR segment occurs in inferior leads.

Abnormal response: With the stable baseline, development of ST-segment slope depression 0.1 mV or more, 80 m.sec after the J point (ST 80) in 3 consecutive beats was considered abnormal. ST 60 measurement was used, if the ST 80 measurement was difficult to interpret due to heart rate>130 beats/min.

The workload was expressed in metabolic equivalents (MET). One MET is equivalent to 3.5 ml O2/kg/min of body weight. The maximum heart rate (MHR) was measured from the formula; MHR = 220 – age in years (± 12 beats/min) [7].

Statistical Analysis

Student't' test and chi-square test were used to assess the significance of difference between mean and proportion respectively. Fisher exact test was used when any one of the expected variables was less than 5. *P* value <0.05 was considered statistically significant. Statistical analysis was carried out using prism graph pad version 9.1.0.

Results

Among 40 cases, 2 patients were eliminated due to their inconclusive treadmill test (TMT).

The age, BMI, and waist-hip ratio (WHR) were comparable among the cases and controls. FBS, PPBS, and HbA1C were significantly raised in cases. Total cholesterol, triglycerides, LDL values showed no difference. The HDL was significantly decreased in cases (*P*<0.001). All other risk factors like hypertension, smoking, family history of ischemic heart disease did not show any significant difference except a family history of diabetes (*P* =0.02). (Table 1)

The TMT was significantly positive among cases than control (*P* = 0.024) (Table 2)

The TMT parameters also showed significant difference between cases and controls. Exercise duration, work load and percentage of target heart rate were significantly lower in cases. (*P*=0.0031, *P*=0.0026, *P*=0.034 respectively) (Table 3)

The patients who were TMT positive were older and males seem to be more affected (*P*=0.0248) than TMT negative patients. However, BMI, WHR, FBS, PPBS, HbA1C, TC, TGL, HDL, LDL did not show any significant difference. The presence of Hypertension and smoking were significantly associated with TMT positive patients (*P*=0.039, *P*=0.047). Family history of IHD, age of onset of diabetes was similar in both groups. The longer duration of diabetes was significantly associated with TMT positive patients (*P*=0.034). (Table 4)

Exercise time and workload were significantly lower in the TMT positive patients (*P*=0.0349, *P*=0.0462). There was no significant difference in the percentage of target heart rate in TMT positive and negative patients. (Table 5)

Table 1: Patient characteristics of study group

Characteristic	CASE N=38	CONTROL N=20	P value
Age (years) mean ± SD	48.14 ± 8.17	46.4 ± 7.04	0.35
Male	21 (55.3%)	12 (60%)	
female	17 (44.7%)	8 (40%)	
BMI (kg/m^2) mean ± SD	25.26 ± 3.14	23.66 ± 2.74	0.06
WHR mean ± SD	0.81 ± 0.09	0.77 ± 0.05	0.08
FBS (mg/dl) mean ± SD	147.24 ± 43.26	78.4 ± 5.59	<0.001*
PPBS (mg/dl) mean ± SD	261.71 ± 99.11	114.1 ± 8.94	<0.0001*
HbA1C (%) mean ± SD	6.23 ± 0.57	4.84 ± 0.21	<0.0001*
TC (mg/dl) mean ± SD	200.82 ± 35.08	205.65 ± 34.71	0.62
TGL (mg/dl) mean ± SD	150.21 ± 66.68	141.65 ± 29.92	0.53
HDL (mg/dl) mean ± SD	28.63 ± 3.74	35.85 ±4.22	<0.001*
LDL (mg/dl) mean ± SD	141.24 ± 35.16	136.45 ± 31.48	0.61
Hypertension	18 (47.4%)	7 (35%)	0.36
Smoking	10 (26.3%)	6 (30%)	0.08
Family history of diabetes mellitus	23 (60.5%)	6 (30%)	0.02*
Family history of IHD	6 (15.8%)	1 (5%)	0.40

BMI- Body mass index, WHR- Waist hip ratio, FBS- fasting blood sugar, PPBS- post prandial blood sugar, HbA1C-Glycated haemoglobin, HDL- High density lipoprotein, TC- Total cholesterol, TGL-Triglycerides LDL- Low density lipoprotein. * represents P <0.05.

Table 2: TMT results in cases and controls:

	Cases	Control	P value
TMT Positive	10 (26.3%)	1 (5%)	0.024*
TMT Negative	28 (73.7%)	19 (95%)	

Table 3: TMT parameters in cases and controls

	Case	Control	P value
Exercise time (minutes) mean ± SD	7.4 ± 1.76	8.83 ± 1.5	0.0031*
Work load (METS) mean ± SD	9.13 ± 2.02	10.89 ± 1.99	0.0026*
Percentage of target heart rate mean ± SD	90.71 ± 8.62	95.15 ± 4.08	0.034*

Table 4: Characteristics of Cases in relation with TMT

Characteristic	TMT Positive N=10 (Male 6 Female 4)	TMT Negative N=28 (Male 15 Female 13)	P value
Age (years) mean ± SD	53.3 ± 7.67	46.64 ± 7.73	0.0248*
Male	6 (60%)	15 (53.6%)	
Female	4 (40%)	13 (46.4%)	
BMI (kg/m^2) mean ± SD	26.32 ± 2.89	24.89 ± 3.19	0.22
WHR mean ± SD	0.78 ± 0.06	0.82 ± 0.10	0.376
FBS (mg/dl) mean ± SD	145.8 ± 33.96	147.75 ± 46.67	0.90
PPBS (mg/dl) mean ± SD	270.4 ± 68.39	258.61 ± 108.92	0.75
HbA1C (%) mean± SD	5.97 ± 0.51	6.33 ± 0.57	0.08
TC (mg/dl) mean ± SD	207.2 ± 40.35	198.54 ± 33.51	0.51
TGL (mg/dl) mean ± SD	177.5 ± 72.0	140.46 ± 63.18	0.13
HDL (mg/dl) mean ± SD	27.5 ± 4.20	29.04 ± 3.55	0.27
LDL (mg/dl) mean ± SD	142.3 ± 40.13	140.85 ± 34.01	0.91
Hypertension	8 (80%)	10 (35.7%)	0.039*
Smoking	5 (50%)	5 (17.8%)	0.047*
Family history of IHD	3 (30%)	3 (10.7%)	0.31
Age of onset of diabetes mellitus (years) mean ± SD	42.4 ± 11.72	41.39 ± 8.74	0.77
Duration of diabetes mellitus (years) mean ± SD	10.6 ± 10.04	5.25 ± 4.99	0.034*

BMI- Body mass index, WHR- Waist hip ratio, FBS- fasting blood sugar, PPBS- post prandial blood sugar, HbA1C-Glycated haemoglobin, HDL- High density lipoprotein, TC- Total cholesterol, TGL-Triglycerides LDL- Low density lipoprotein. * represents P <0.05.

Table 5: TMT parameters in cases

	TMT positive	TMT negative	P value
Exercise time (minutes) mean ± SD	6.38 ± 1.31	7.73 ± 1.77	0.0349*
Work load (METS) mean ± SD	8.04 ± 1.46	9.51 ± 2.07	0.0462*
Percentage of target heart rate mean ± SD	93.1 ± 6.98	89.86 ± 9.10	0.313

Discussion

The worldwide explosion of diabetes mellitus will be centered in the developing countries due to the increase prevalence of Type 2 diabetes mellitus. The prevalence of CAD in patients with T2DM in southeast Asia was 29.4%, the highest among the world [10]. This is mainly due to pathophysiological and lifestyle changes [11].

The prevalence of silent myocardial ischemia was 26.3% in patients with T2DM and 5% in controls in our study. This showed, SMI was more common in T2DM. The prevalence of silent myocardial ischemia varies between 10 to more than 50% in various studies. This is due to the various definitions of SMI, various methodology, presence of comorbidities, and duration of diabetes mellitus [12]. The prevalence of SMI was 22% in the first large prospective DIAD study [13].

In our study, there was no significant difference in the age group between cases and control(*P* =0.35). But, the significant difference was noted between TMT positive and TMT negative group (*P*=0.0248). Age is an important risk factor for CAD. Our study finding was similar to other studies [14]. Few studies didn't find any correlation between age and CAD in patients with diabetes mellitus [15,16].

In our study, SMI is more common in males (60%) than females (40%). CAD is more common in males than females. Along with smoking, hypertension, absence of the protective role of oestrogen, and stress-related factors males are more prone to CAD. So many studies proved that males are more prone to CAD [13,17,18].

Various studies reported a positive correlation between BMI and CAD [15,19]. Glogner et al found that prevalence of myocardial infarction increased in proportion up to BMI of 30, followed by a paradoxical decrease in myocardial infarction prevalence beyond BMI of 40 [20]. In our study, BMI and WHR were higher in patients with diabetes than in control. No significant difference was noted between cases and controls as well as in TMT positive and TMT negative groups. Indians are more prone to diabetes with normal BMI and thin phenotype [21]. Along with this small sample size may be the reason for this finding in our study.

Prevalence of SMI in newly detected T2DM was 10% and 44% in patients with more than 10-year duration. As the duration increases, the prevalence also increases eventually. This finding correlates with other studies [18,22].

Hypertension is well-known risk factor for CAD. In our study, the prevalence of the hypertension among patients with T2DM was 47.4%. Hypertension was present in 80% of TMT positive. A similar finding was found in other studies also [18,22].

In this study, smoking history was present in 26% of T2DM and 30% of non-diabetic. But in TMT positive group,50%were smokers compared to 18% in TMT negative group. Smoking increases the risk of CAD in diabetes mellitus [18].

Our study population showed characteristic lipid abnormality of diabetes with normal or slightly raised total cholesterol, TGL, and low HDL levels [23]. There was no significant difference noted between diabetics and control in total cholesterol, LDL, and TGL level. But, significant difference was noted in HDL level between T2DM and control (*P*<0.001). But, no difference was noted in lipid profile between TMT positive and TMT negative groups. Despite that 26.3% of T2DM developed silent myocardial ischemia. This shows that other than lipid profile, various factors like hypertension, smoking, duration of diabetes, and lifestyle behaviour play a major role in coronary artery disease. Drugs like statins also might have affected the lipid profile in our study population. In our study, a significant difference was observed between cases and control (*P*=0.0031) as well as between TMT positive and negative group (*P*=0.0349); which showed exercise time was significantly reduced in patients with diabetes especially in those with SMI. The relative risk increases from 6.7 to 14.7 and 3.6 to 5.6 in males and females respectively, if the ST depression occurs at 5 minutes of exercise [24].Diabetic patients with higher workloads on Exercise ECG (≥10 METs) have a low risk of future cardiac events. In our study, a significant difference was noted between cases and control (P=0.0026), as well as between TMT positive and negative group (P=0.0462); which showed, patients with diabetes had low exercise capacity compared to the normal population especially those with SMI. TMT positive group had a mean workload of 8.04 which made them high risk as per Bourque et al study [6].

Heller et al found that achieving only 70% of maximum heart rate causes a spurious reduction in the stress defects incidence and angina by 47% and 26% respectively [25]. In our study, there was a significant difference between control and cases (P=0.034) but not in between TMT positive and negative group (P=0.313). These TMT parameter findings correlated well with the study done by Chauhan et al [26].

In our study, there was no correlation between blood sugar, HbA1C, and family history of IHD. Delenne et al found correlation a between family history of IHD and SMI but not with HbA1C level [17].

Conclusion

The prevalence of SMI is higher in a patient with diabetes than a non-diabetic healthy population. Prevalence of SMI increases in proportion with the duration of diabetes mellitus. Hypertension and smoking amplify the risk of CAD in diabetes mellitus.

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