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ORIGINAL RESEARCH

Evaluation of Asymptomatic Ischaemic Heart Disease in Type 2 Diabetes Mellitus patients by Exercise Treadmill Test and Correlation with Various Risk Factors of Coronary Vascular Disease

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Abstract

Introduction: Diabetic patients sometimes do exhibit silent ischemia because of the occurrence of neuropathy of the thoracic nerve fibers due to which they do not reveal the classical signs of angina. Therefore, the present study is designed to demonstrate the usefulness of exercise treadmill test for early detection of asymptomatic ischemic heart disease in type 2 diabetes mellitus.

Material and Methods: The present study was carried among 180 patients of type 2 diabetes mellitus who were evaluated for the presence of silent myocardial ischemia by using exercise treadmill test (TMT). The depth of the ST segment depression and the time needed for the recovery of ECG changes was noted. Chi square test, Whitney Test and Fisher Exact test were applied for statistical significance.

Results: The study revealed that 43 patients (23.89%) out of 180 diabetic patients had silent myocardial ischemia. Silent myocardial ischemia was found to be related with duration of diabetes mellitus. Proportion of exercise treadmill test (positive) was significantly higher in patients who had diabetes mellitus for 11-15 years as compared to patients who had DM for <=5years and 6-10 years (100% vs 11.32%, 29.51% respectively) (p value <.0001). Median of HbA1c (%) in positive exercise treadmill test was 10 (9-11.05) which was significantly higher as compared to negative exercise treadmill test 7.5 (7-8.2). (p value<.0001).

Conclusion: Determining silent myocardial ischemia in diabetic patients is important due to high morbidity and mortality of IHD in diabetic patients. Duration of diabetes mellitus, dyslipidemia, glycosylated haemoglobin, BMI, hypertension, family history of diabetes mellitus are strong clinical predictors of silent myocardial ischemia. Longer the duration of diabetes mellitus, greater the risk of silent myocardial ischemia.

Keywords: Cardiovascular diseases; Ischemia; Neuropathy

Introduction

Diabetic neuropathy (DN) is the most usual complication of diabetes which is typified by damage to nerve glial cells, their axons along with endothelial cells.[1] Diabetic patients sometimes do exhibit silent ischemia as they not reveal the classical signs of angina because of the occurrence of neuropathy of the thoracic nerve fibres. Clinical studies have reported an association between silent myocardial infarction and ischemia and autonomic neuropathy.[2-5] Thus, this may eventually present with sudden death, myocardial infarction, arrhythmias or

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heart failure leading to premature deaths. Therefore, screening for early detection of asymptomatic ischaemic heart disease in patients with type 2 diabetes may be helpful to prevent these catastrophic cardiac events and consequent deaths. However periodical clinical examination and resting electrocardiogram (ECG) are not useful for this purpose as many times these methods fail to detect asymptomatic ischaemic heart disease. American Diabetic Association (ADA) recommends the use of exercise treadmill test and coronary angiography for the diagnosis of silent ischaemia.[6,7]

Exercise treadmill test is a non-invasive test which can be carried out on OPD basis. It can identify the majority of patients likely to have significant ischemia during their daily activities.[8]It is important to adapt appropriate criteria for selecting high risk patients who would benefit most from the routine ischemic heart disease (IHD) screening. The IHD screening results might identify the individuals who could benefit from Anti Ischemia therapy{medical management or invasive management}. The screening results can influence the physician's advice for the patient and the treatment targets for ischemia.[9] Therefore, the present study is designed to demonstrate the usefulness of exercise treadmill test for early detection of asymptomatic ischemic heart disease in type2 diabetes mellitus.

Material and Methods

The present hospital based descriptive study was commenced among 180 type-2 Diabetes Mellitus patients who visited the Internal Medicine Department a Guru Gobind Singh Medical College and Hospital either via outpatient clinic or via in-patient department. The study was initiated after obtaining ethical clearance from the ethical committee of our institute and participants were enrolled after obtaining written and informed consent from them. The participants were selected using consecutive sampling technique. The inclusion criteria comprised of patients with type2 diabetes mellitus aged between 35-65years, of any gender who are willing to participate in the current study. The exclusion criteria consisted of patients with known case of ischemic heart disease, patients having other heart disease like valvular heart disease, cardiomyopathy, congenital heart disease and pericardial disease and patients who had contraindications to undergo exercise treadmill test.

Patients who satisfied the inclusion and exclusion criteria were selected. Written and informed consent was taken from each patient. Detailed history and thorough clinical examination were done as per the attached pro forma. The study subjects were then evaluated for the presence of silent myocardial ischemia by using exercise treadmill test (TMT). All the subjects underwent treadmill test which was performed on RMSTMT MarkII as per to the standard of Bruce protocol. The results obtained will be tabulated and analyzed using appropriate statistical tools.

Electrocardiographic stress testing was done. ECG was recorded before, during and after exercise on a treadmill. The test consists of incremental increase in external workload while symptoms, the ECG and blood pressure are monitored. Exercise duration was symptom limited, and the test was discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST segment depression >0.2Mv(2mm), a fall in systolic blood pressure >10mmHg or the development of ventricular tachyarrhythmia.

The ischemic ST-T response which is defined as flat or down sloping depression in ST segment >0.1Mv below baseline (i.e., the P-R segment) and lasting longer than 0.08s were noted. Up sloping or junctional ST segment changes were not considered characteristic of ischemia as they do not constitute a positive test. Although T wave abnormalities, conduction disturbances and ventricular arrhythmias that develop during exercise were noted. Negative exercise test in which target heart rate was not achieved (85% of the maximum predicted heart rate for age and sex) were considered non diagnostic.

In interpreting ECG stress tests, the probability that CAD exists in the patient or population

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under study (i.e., pretest probability) should be considered.
A medical professional was present throughout the treadmill test. The total duration of exercise, the times to the onset of ischemic ST-T changes and chest discomfort, the external work performed(expressed as stage of exercise)and the internal cardiac work performed i.e., by the heart rate-blood pressure product were measured. The depth of the ST segment depression and the time needed for the recovery of ECG changes was noted.
The data pertaining to socio-demographic and other clinical and NCS variables were entered as a data matrix in Microsoft® Excel® and analysed using IBM® SPSS® software version 20.0.0 in the light of suitable statistical tests. Chi square test, Whitney Test and Fisher Exact test were applied for statistical significance.

Results

Table1: association of age (years) with exercise treadmill test

Parameters		Negative (n=137)	Positive (n=43)	Total	P value	Test performed
Age (years)	<=40	33 (94.29%)	2(5.71%)	35 (100%)	<.0001	Chi squaretest,27.246
	41-50	48 (87.27%)	7(12.73%)	55 (100%)		
	51-60	42 (71.19%)	17 (28.81%)	59 (100%)		
	>60	14 (45.16%)	17 (54.84%)	31 (100%)		
	Mean±SD	49.02± 8.65	56.98± 7.14	50.92± 8.97	<.0001	Mann Whitney test; 1411.5
	Median(25th-75th percentile)	48 (42-56)	58 (54-62)	50.5 (43-58)		
	Range	35-65	35-65	35-65		
Gender	Female	51 (77.27%)	15 (22.73%)	66 (100%)	0.781	Chi squaretest,0.077
	Male	86 (75.44%)	28 (24.56%)	114 (100%)		
	Total	137 (76.11%)	43 (23.89%)	180 (100%)		

Proportion of exercise treadmill test (negative) was significantly higher in<=40years, 41-50years, 51-60years of age as compared to>60years (94.29%, 87.27%, 71.19% vs 45.16% respectively) and positive exercise treadmill test was significantly higher in >60years as compared to <=40years, 41-50years and 51-60years (54.84% vs 5.71%, 12.73%, 28.81% respectively) (p value <.0001). Median (25th-75th percentile) of age(years) in positive exercise treadmill test was 58(54-62) which was significantly higher as compared to negative exercise treadmill test 48(42-56)) (table 1). Distribution of exercise treadmill test (negative and positive) was comparable in female and male (negative:77.27% vs 75.44% respectively) and (positive: 22.73% vs 24.56% respectively) (p value =0.781) (table 1).

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Table 2: Association of duration of diabetes (years) and **treatment modality with exercise treadmill test**

Parameters		Negative (n=137)	Positive (n=43)	Total	P value	Test performed
Duration of diabetes(years)	<=5 years	94 (88.68%)	12 (11.32%)	106 (100%)	<.0001	Fisher Exact test
	6-10years	43 (70.49%)	18 (29.51%)	61 (100%)		
	11-15years	0(0%)	13 (100%)	13 (100%)		
	Mean±SD	4.35± 2.16	8.35± 3.5	5.31± 3.06		
	Median(25th-75th percentile)	4(3-6)	8(5-11)	5(3-7)	<.0001	MannWhitneytest;1032.5
	Range	0.25-10	2-15	0.25-15		
Treatment modality	Insulin	6(60%)	4(40%)	10 (100%)	0.253	Fisher Exact test
	Oral hypoglycemic agent	131 (77.06%)	39 (22.94%)	170 (100%)		
	Total	137 (76.11%)	43 (23.89%)	180 (100%)		

Proportion of exercise treadmill test (positive) was significantly higher in 11-15 years as compared to ≤5years and 6-10 years (100% vs 11.32%, 29.51% respectively) (p value <.0001). Median (IQR) of duration of diabetes (years) in positive exercise treadmill test was 8(5-11) which was significantly higher as compared to negative exercise treadmill test 4(3-6)) (table 2). Distribution of exercise treadmill test (negative and positive) was comparable in insulin and oral hypoglycemic agent (negative: 60% vs 77.06% respectively) and (positive:40% vs 22.94% respectively)(p value=0.253) (table 2).

Proportion of exercise treadmill test (positive) was significantly higher in dyslipidemia(79.49%, p value <.0001), hypertension (41.94%, p value<.0001) and alcohol (41.67%,p value<.0001) (table 3).

Table 3: Association of risk factors with exercise treadmill test

Risk factors	Negative (n=137)	Positive (n=43)	Total	P value	Test performed
Hypertension	54 (58.06%)	39 (41.94%)	93 (100%)	<.0001	Fisher Exact test
Smoking	17 (65.38%)	9 (34.62%)	26 (100%)	0.166	Chi square test,1.923
Alcohol	35 (58.33%)	25 (41.67%)	60 (100%)	<.0001	Chi square test,15.644
Dyslipidemia	8 (20.51%)	31 (79.49%)	39 (100%)	<.0001	Chi square test,84.644

Table 4: Association of glycemic parameters with exercise treadmill test

Glycemic parameters	Negative (n=137)	Positive (n=43)	Total	P value	Test Performed
HbA1c (%)					

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Mean ±SD	7.65± 0.95	9.97± 1.51	8.2 ± 1.48		
Median(25th-75th percentile)	7.5 (7-8.2)	10 (9-11.05)	7.85 (7.2-9)	<.0001	MannWhitneytest;640
Range	5.6-10.6	6.6-12.6	5.6-12.6		
Fasting blood sugar (mg/dL)					
Mean ±SD	146.18± 27.73	162.65± 24.7	150.11± 27.87		
Median (25th-75thpercentile)	143 (127-164)	158 (144-175.5)	146 (132-166)	0.0004	MannWhitney test;1881.5
Range	86-244	122-244	86-244		

Median (IQR) of HbA1c (%) in positive exercise treadmill test was 10(9-11.05) which was significantly higher as compared to negative exercise treadmill test 7.5(7-8.2). (p value<.0001). Median (IQR) of fasting blood sugar(mg/dL) in positive exercise treadmill test was 158(144-175.5) which was significantly higher as compared to negative exercise treadmill test 143(127-164) (p value=0.0004) (table 4).

Table 5: Multivariate logistic regression for predicting independent risk factors of positive exercise treadmill test

Exercise treadmill test	Beta coefficient	Standard error	P value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound(95%)
Age(years)	0.025	0.053	0.637	1.025	0.924	1.138
Bodymass index(kg/m²)	0.227	0.174	0.192	1.255	0.893	1.764
Duration of diabetes(years)	0.156	0.154	0.313	1.168	0.863	1.581
Systolic blood pressure (mm/Hg)	0.036	0.043	0.393	1.037	0.954	1.127
Diastolic blood pressure(mm/Hg)	0.064	0.052	0.217	1.066	0.963	1.180
HBA1C(%)	0.803	0.341	0.018	2.233	1.145	4.354
Cholesterol(mg/dL)	0.021	0.022	0.328	1.022	0.979	1.066
Triglycerides mg/dL)	0.008	0.010	0.416	1.008	0.989	1.027
High density lipoprotein (mg/dL)	-0.168	0.105	0.108	0.845	0.688	1.038
Low density lipoprotein (mg/dL)	-0.023	0.020	0.249	0.978	0.941	1.016
Very low density lipoprotein (mg/dL)	0.082	0.056	0.142	1.085	0.973	1.211
Fasting blood sugar(mg/dL)	0.011	0.013	0.379	1.011	0.986	1.037
Family history of IHD	1.092	1.281	0.394	2.980	0.242	36.668
Hypertension	0.618	0.947	0.514	1.855	0.290	11.865
Alcohol	-0.150	0.815	0.854	0.861	0.174	4.254
Dyslipidemia	1.498	1.156	0.195	4.472	0.464	43.079

On performing multivariate logistic regression, HbA1c (%) was the only significant

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independent risk factor of positive exercise treadmill test with adjusted odds ratio of 2.233 (table 5).

Discussion

Given the prevalence of IHD in patients with type2 diabetes, the American Diabetes Association (ADA) recommends performing a cardiovascular risk assessment every yearly. In addition, ADA recommends exercise testing in all asymptomatic patients with diabetes.[10] The optimal frequency of stress testing is unknown, although it has been suggested that stress testing should be considered every 3-5 years for asymptomatic patients with no new risk factors.[11] For patients with multiple or new risk factors, testing should be increased to every 1-2 years. Identification of diabetic patients with early CAD allows for risk stratification at a point where disease process is more likely to be modifiable.[12]Thisisutmost important, since the aggressive use of secondary interventions has been proven to reduce morbidity and mortality.[13] Hence, the present study was undertaken to evaluate asymptomatic ischemic heart disease in type 2 diabetes mellitus patients by exercise treadmill test and to correlate various risk factors of coronary vascular disease with asymptomatic ischemic heart disease identified by this test.

The current study was conducted in the Department of Medicine, among 180diabeticpatients, with variable degrees of glycemic control who were enrolled in the study after ruling out any clinical evidence of myocardial ischemia i.e., the diabetic patients included in the study were completely asymptomatic for ischemic heart disease. The study subjects were then evaluated for the presence of silent myocardial ischemia by using exercise treadmill test. Among 180 patients, 66 were females and 114 were males. The higher percentage of male patients in the study could be due to random selection of study subjects. The mean age of the study population was 51.04 ± 9.4 years; with minimum age of 35 years and maximum age of 65 years.

It was found in the present study that the patients with positive exercise treadmill test were significantly higher in the >60 years group (58.84%), followed by the 51-60 years group (28.81%) and < 50 years age group (12.73%). Similar to our study, Valensi Pet al[14]conducted a study in which it was found that in asymptomatic diabetic patients with additional cardiovascular risk factors, silent myocardial ischemia (SMI) is a potent predictor of cardiac events and should be assessed preferably in the patients >60years of age. Another study was commenced by Callaham PR et al[15] to determine the prognosis of silent ischemia in an unselected group of patients referred for exercise testing, and to assess whether age or the presence of myocardial infarction or diabetes mellitus influences the prevalence of silent myocardial ischemia during exercise testing and it was found that increasing age was associated with higher prevalence of silent ischemia.

In the present study, out of total 180 patients, exercise treadmill test was positive in 43 patients(23.89%). The prevalence of silent myocardial ischemia reported in our study was comparable to the studies conducted earlier. In one of the comparable studies, Kawano Y et al[16] screened 128 asymptomatic patients with T2DM without previous histories of CVD for the detection of silent myocardial ischemia in diabetic patients without previous history of cardiovascular disease and was able to detect 24patients(19%) who were having coronary fractional flow reserve. Similarly, Langer A et al[17] conducted a study for detection of silent ischemia in diabetic patients by exercise treadmill test and reported the prevalence of silent myocardial ischemia as 17% i.e., 10out of 58 patients. According to previous studies, in non-diabetic populations, the prevalence of silent ischemia varies from 0.5% to 15% which is less as comparative to diabetic patients; hence there is high risk in diabetic patients. Moreover, May O et al[18]commenced a study to find prevalence and prediction of silent ischemia in diabetics and non-diabetics and observed prevalence of silent ischemia in diabetics was

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13.5% and in non-diabetics it was 6.4%. Another study was conducted by Lubaszewski W et al[19] in which reported prevalence of silent ischemia in diabetic patients was 29.3% as compared to 12.5%in non-diabetic patients. Furthermore, as per the previous data, the prevalence of SMI has a broad range from 6.4-56.7% in diabetic population.[20,21] The broad range may be related to the characteristics of study population-age, gender, type of diabetes, duration of diabetes, presence of micro vascular and macro vascular complications.

In our study population, maximum number of patients (106/180) had duration of diabetes less than 5 years with positive TMT in 12, 61patients had duration of diabetes between 6-10 years with positive TMT in 18 and 13 patients had duration of diabetes between 11-15 years with positive TMT in13. Hence, the patients having duration of diabetes longer than 5 years were found to have more prevalence of silent myocardial ischemia. These results were consistent with previous studies. Comparable to our study, Sargin Het al[22] assessed 500 patients with type 2 diabetes mellitus with normal resting ECG and found that 62 (12.4%) patients had asymptomatic myocardial ischemia on exercise treadmill testing and these abnormalities of exercise test were associated with longer duration of diabetes. In another study, conducted by Venuraju SM et al[21] to predict significant CAD in patients with T2DM and investigated whether clinical and demographic characteristics can be used to calculate significant changes in these patients and concluded that routine screening for CAD using computed tomography coronary angiography (CTCA) should be considered for patients with a diagnosis of T2DM for > 10.5 years and SBP > 140 mm Hg which is considered like our study that there is more prevalence of silent myocardial ischemia in patients with duration f diabetes longer than 5 years.

Increased levels of glycosylated hemoglobin indicates poor glycemic control and it has a great influence on coronary artery disease.[23] In our study, median of HbA1c in patients with positive exercise treadmill test was 10 (9-11.5) which was significantly higher as compared to negative exercise treadmill test. Similarly, median of fasting blood sugar in positive treadmill test was 158 (144-175) which was significantly high as compared to negative exercise treadmill test. Furthermore, on performing multivariate logistic regression, HbA1c (%) was the only significant independent risk factor of positive exercise treadmill test with adjusted odds ratio of 2.233 which is upheld by other studies revealing poor glycemic control has influence on coronary artery disease. In a study carried by Ravipathi G et al,[24]coronary angiography was performed among diabetes mellitus patients who reported because of chest pain and it was revealed that significant increasing trend of haemoglobin A1c levels were found over the increasing number of coronary vessel involvement with CAD. Similar to this, another large prospective cohort study commenced by Elley CR et al[25] confirmed that increased HbA1c is an independent risk factor for cardiovascular disease after controlling for traditional risk factors.

Moreover, another like study by Zellweger MJ et al[26] that assessed predictors revealed that male sex, diabetes duration, peripheral artery disease, smoking, elevated systolic blood pressure and increased brain-natriuretic peptides independently predicted silent coronary artery disease (SCAD) and concluded that in presence of >3 predictors, almost 50% of patients had an abnormal myocardial perfusion scintigraphy(MPS). Thus, it was observed from the current study that asymptomatic ischemic heart disease or silent myocardial ischemia exists in significant proportion of diabetic patients especially in those with concurrent risk factors like systolic hypertension, dyslipidemia, positive family history and obesity. Hence screening of these patients for inducible ischemia by non-invasive testing such as exercise treadmill test is a needed priority.

The major limitation of the study is that only non-invasive exercise treadmill test was done for the detection of silent myocardial ischemia. Coronary angiography was not performed in the study subjects. It is possible that some subjects with negative exercise treadmill test result

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could still have significant stenosis of coronary arteries.

Conclusion

Determining silent myocardial ischemia in diabetic patients is important due to high morbidity and mortality of IHD in diabetic patients. The study consisted of two aspects; the prevalence of silent myocardial ischemia in asymptomatic patients with diabetes mellitus and assessment of the clinical predictors of silent myocardial ischemia in these patients. Duration of diabetes mellitus, dyslipidemia, glycosylated hemoglobin, BMI, Hypertension, family history of diabetes mellitus are strong clinical predictors of silent myocardial ischemia. Longer the duration of diabetes mellitus, greater the risk of silent myocardial ischemia.

An approach based on risk factors is recommended as a part of initial diagnostic evaluation to detect IHD in asymptomatic patients with diabetes. Patients at low risk can be managed medically without additional testing, while patients with advanced disease may require revascularization procedures that could prolong life. Once asymptomatic CAD is diagnosed, physicians should recommend patients adherence to risk factor intervention and treatment regimens.

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