A Prospective Study on Utility of Exercise Treadmill Test in Type 2 Diabetes Mellitus Patients

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Abstract

Objective: Primary objective of this study was to assess utility of exercise treadmill test in type-2 diabetes mellitus patients for detecting silent myocardial ischaemia and associated risk factors.

Method: 75 DM-2 cases were enrolled in study of any age attending medical OPD. All cases were gone through detailed history and TMT procedure.

Result: There is higher prevalence of SMI in DM-2 patients. TMT positivity for inducible ischaemia in DM-2 patients were associated with increasing age, male sex, higher BMI, hypertension, smoking, alcoholism, microalbuminuria, macroalbuminuria and dyslipidemia. Duration of diabetes increases the development of CAD in diabetic patients. TMT is a safe procedure with no complication.

Conclusion: For detection of silent myocardial ischaemia in diabetic patients TMT has a significant role. Prevalence of silent myocardial ischaemia in DM-2 patients is 37.3%. There is significant correlation between risk factors of CVD and evidence of ischaemia on TMT in diabetic patients. Duration of diabetic state has a strong correlation for inducible ischaemia on TMT. It may be a safer, cheaper, reliable and easily available non-invasive screening tool for earlier detection of CAD in diabetic patients.

Editorial Viewpoint

• There is high incidence of silent ischemia in patients with type 2 DM.
• There is need of cheap safe and easily available test for detection of CAD as patients are at high risk of cardiac mortality.
• TMT continues to be of utility in diabetic patients and there is higher prevalence of TMT positivity correlating with other risk factors.

Introduction

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia and accompanied by other biochemical disturbances and the presence of progressive diabetic tissue damage with micro and macrovascular complications. It is projected that 366 million people will be diabetic in 2030, 290 million of whom will be living in developing countries.

Type 2 DM is a Framingham risk factor for CAD and have a higher prevalence of IHD. The Framingham study has shown that cardiovascular mortality is twice in diabetic men and four times in diabetic women as compared with non-diabetic counter parts. Prevalence of angina pectoris is 60% greater in diabetic men and 90% greater in diabetic women than in a non-diabetics. Incidence of left main coronary artery is higher (13%) in diabetic versus non-diabetic (60%), sudden death occurs 50% more in diabetic men and 30% more in diabetic women.

Diabetic patients may not exhibit the classic symptoms of angina because of the presence of neuropathy involving the thoracic nerve fibres and this is referred to as ‘Silent Ischaemia’ so have a higher cardiac mortality risk and prevalence than those with symptomatic CAD. American Diabetic Association recommends use of TMT and coronary arterial angiography for diagnosis of silent ischemia that is useful initial diagnostic test in patients with an intermediate pretest probability (25%–75%) of coronary artery disease. It is cheaper, relatively safe, widely and easily available noninvasive diagnostic test which act as an important
link between other investigations such as ECG, Echocardiography, other non-invasive stress imaging technologies such as stress echocardiography, stress SPECT myocardigraphy and confirmatory coronary angiography for screening, detection and appropriate management of CAD and SMI that can be repeated every 2-3 yearly in high risk groups. According to Dr. Lisa Walters, 2009, mean sensitivity is 68% and mean specificity is 77%, while Gianrossi R, et al, 1989 results showed sensitivity of 50% and a specificity of 90%.

Given the high prevalence of both NIDDM and IHD among Indian and the younger age of onset of diabetes and the associated risk factors we thought to study the utility of treadmill test in screening of IHD in DM-2 patients.

Material and Methods

Study Objectives: Objectives of this study was to assess Role of TMT and prevalence of SMI in DM-2 patients, to ascertain any correlation between risk factors of CVD and evidence of ischaemia on TMT, to assess correlation in duration of diabetic state suggestive of coronary ischaemia on TMT and to find out the safety and reliability of TMT in Type-2 DM-2 patients.

Study Population: 75 DM-2 cases without established clinical diagnosis of coronary artery disease attending medicine OPD at New Medical College Hospital, Govt. Medical College, Kota, Rajasthan, during December 2013 to January 2015 are enrolled in the study. Subjects were assigned to three Groups. Group-1 (n=25): Cases who had no symptoms suggestive of CAD and who had a normal ECG, Group-2 (n=25): Cases who were asymptomatic but resting ECG shows some abnormality (ST-T changes), Group-3 (n=25): Cases who were symptomatic for CAD (typical or atypical) with either Normal or Abnormal resting ECG

Inclusion criteria: By using simple random method 75 individual of Type-2 Diabetes Mellitus patients diagnosed by ADA criteria of any age, sex and any duration of Type-2 Diabetes Mellitus, taking any form of treatment, who give consent and suitable to do TMT were included in this study.

Exclusion criteria: Individuals with documented myocardial infarction, unstable angina, left bundle branch block, severe left ventricular hypertrophy, valvular heart disease, cardiomyopathy, uncontrolled hypertension, hemodynamically unstable patients and those who had undergone angioplasty, coronary artery bypass surgery are not included. Patients with severe osteoarthritis or other disabilities (who are unable to perform test), advanced diabetic disease with unstable complication, anaemia, other known absolute and relative contraindications of TMT, inconclusive test result for TMT and patients not willing to give consent are excluded.

Detailed history of presenting complain and emphasis on cardiac symptoms analysis and past history of HTN, IHD, CVA and O.A. with emphasis on duration of type 2 diabetes with treatment history and personal history of substance abuse were taken. A complete physical examination with a detailed cardiovascular assessment and evaluation of peripheral pulses are done in all cases. The blood pressure was recorded in both supine and standing postures.

The laboratory investigations include CBC, ESR, Urine routine and for Qualitative Micro/Macro albuminuria, fasting and postprandial plasma glucose estimations, serum creatinine, blood urea and a complete lipid profile. All individuals underwent a resting 12 lead ECG and X-ray chest PA view prior to performing the TMT. Another ECG recorded during 20-30 seconds of hyperventilation as this procedure can produce ECG changes similar to ischemic patients. Appearance of such changes suggest the increased possibility of false positive test results. Risk factors evaluated as HTN, obesity, dyslipidemia, smoking, microalbuminuria, macroalbuminuria, creatinine, physical activity in form of morning walk or jogging.

A history elicited from all patients for duration of diabetes mellitus. Height and weight were measured for Body mass index (BMI) that was calculated by Quetelet’s formula and subjects are accordingly categorized (normal=18.5-24.9, overweight=25-29.9, obese=30-39.9). Autonomic functions were not evaluated.

The TMT was done using a computerized CTMT Machine-Model Norav-1200-S, Make Instromedix India Pvt. Ltd. with built-in protocols. Continuous ECG recordings were taken. Exercise test terminated in all patients following the achievement of target heart rate, any arrhythmia or an abnormal ischemic response in form of relatively flat or downsloping ST segment depression (≥1 mV/sec) after the J point in three consecutive beats with a stable baseline. Exercise test was also terminated if patient developed dyspnea, fatigue or chest pain and hypertensive response.

Statistical Analysis: Statistical methods used were unpaired student’s t-test for continuous variables, chi-sq test for categorical variables using Microsoft excel and spss version 16. A value of p>0.05 is considered as not significant, p≤0.05 as significant, p<0.001 as highly significant, p<0.0001 as very significant.

Result

Total number of 75 cases included in this study. Mean age of study subjects (Mean age ± SD) in group-1 was 52.96±9.99 years, in group-2 was 52.84±8.45 years and in group-3 was 51.36±9.8 years and most of cases belongs to 40-60
In all the cases subjects were known to have diabetes mellitus type-2 and were taking OHA treatment. There were 32 males and 21 females having DM-2 since 1-5 years and 15 males and 7 females having DM-2 since 6-10 years.

Blood sugar fasting (BSF) was ranging 96-267 mg/dL (mean 147.9) and post prandial (BSPP) was 126-328 mg/dL (mean 234.5) in group-1, BSF ranging 87-155 mg/dL (mean 107.8) and BSPP was 120-244 mg/dL (188.6) in group-2 and range of BSF was 84-339 mg/dL (mean 140.7) and BSPP was 120-350 mg/dL (mean 217.2) in group-3. Blood urea was 13-55 mg% (mean 28.8) and serum creatinine was 0.7-1.1 mg% (mean 0.88) in group-1 cases, blood urea 15-40 mg% (mean 27.2) and serum creatinine 0.7-1.1 mg% (mean 0.88) in group-2 cases and blood urea 10-44 mg% (mean 32.6) and serum creatinine was 0.7-1.1 mg% (mean 0.89) in group-3 cases.

Haematological parameters were in normal range in all cases.

Urine microscopic examination in all cases were with in normal limits. Microalbuminuria was present in 23 (30.6%) cases and macroalbuminuria was present in 12 (16%) cases. Resting ECG in all cases of group-1 were normal, in group-2 all cases having ECG abnormality in form of minor ST-T changes and in group-3 have 16 cases normal and 9 cases has ST-T changes.

Asymptomatic and ECG normal
Group-1 (n=25)

Mean Age in years 52.96
Sex M=15 (60%), F=10 (40%)
BMI ≥30 8 (32%)
BMI <29.9 17 (68%)
Hypertensive 14 (56%)
Alcoholic 5 (20%)
Smoker 10 (40%)
Duration of DM-2 (1-5 years) M=7 (28%), F=3 (12%)
Duration of DM-2 (6-10 years) M=8 (32%), F=2 (8%)
BSF (mg/dL) 84-339 (mean 107.8)
BSPP (mg/dL) 120-350 (mean 217.2)

Asymptomatic and ECG normal
Group-2 (n=25)

Mean Age in years 52.84
Sex M=14 (56%), F=11 (44%)
BMI ≥30 5 (20%)
BMI <29.9 20 (80%)
Hypertensive 14 (56%)
Alcoholic 3 (12%)
Smoker 10 (40%)
Duration of DM-2 (1-5 years) M=7 (28%), F=7 (28%)
Duration of DM-2 (6-10 years) M=4 (16%), F=2 (8%)
BSF (mg/dL) 104.2-217.2 (mean 188.6)
BSPP (mg/dL) 120-244 (mean 234.5)

Asymptomatic and ECG normal
Group-3 (n=25)

Mean Age in years 51.36
Sex M=16 (64%), F=9 (36%)
BMI ≥30 6 (24%)
BMI <29.9 19 (76%)
Hypertensive 14 (56%)
Alcoholic 6 (24%)
Smoker 13 (52%)
Duration of DM-2 (1-5 years) M=13 (52%), F=7 (28%)
Duration of DM-2 (6-10 years) M=3 (12%), F=2 (8%)
BSF (mg/dL) 179 ± 47.50
BSPP (mg/dL) 27.2 ± 12.05

Table 3: Silent ischaemia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=25)</th>
<th>Group 2 (n=25)</th>
<th>Group 3 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic and ECG normal</td>
<td>9 (44.5%)</td>
<td>3 (33.3%)</td>
<td>10 (60%)</td>
</tr>
<tr>
<td>Symptomatic and ECG normal</td>
<td>5 (55.5%)</td>
<td>6 (66.7%)</td>
<td>6 (60%)</td>
</tr>
</tbody>
</table>

X-ray chest P.A. view of all cases was normal.

In group-1 (n=25) 9 cases (36%) were TMT positive, in group-2 (n=25) 9 cases (36%) were TMT positive and in group-3 (n=25) 10 cases (40%) were TMT positive. In group-3 10 cases were TMT positive in which 6 have normal ECG and 4 have ST-T changes while in 15 TMT negative cases 10 have normal ECG and 5 have ST-T changes.

Mean age of TMT Positive and TMT negative were 56.1±7.71 years and 51.1±9.59 and it was significant as p-value is 0.0032.

TMT positivity in males was 40%, 50% and 50% in group 1, 2 and 3 respectively and in females were 30%, 18.1% and 22.2% in group 1, 2 and 3 respectively with a significant p-value (0.0042).

Out of the 75 patients studied, only 3 (4.0%) developed complications in form of ventricular ectopics. There are 1 patients who developed moderate angina but that relief with sublingual nitrate. There was no instance of TMT induced myocardial infarction or death in our study.

Cases having microalbuminuria in TMT positive and negative were 57.1% and 14.9% respectively, statistical data showing very significant association (p value = 0.00007). Whereas macroalbuminuria in TMT positive and negative were 28.5% and 8.5% respectively, statistical data showing significant association (p value = 0.021).

Out of TMT positive cases 67.8% were smoker while 32.2% cases were non-smoker. In TMT negative cases 29.7% were smoker and 70.3% were non-smoker. Out of TMT positive cases 38 (71.7%) were smoker while 32.2% cases were non-smoker. In TMT negative cases 29.7% were smoker and 70.3% were non-smoker.
were non-smoker. Statistically data showing very significant correlation. (p value=0.00000062). 78.5% were alcoholic and 21.5% were non-alcoholic in TMT positive cases while in TMT negative cases 27.8% were alcoholic and 72.2% were non-alcoholic, showing highly significance p-value (0.0004). In TMT positive cases 39.3% were obese and in TMT negative cases 17% were obese, showing significant data (P< 0.05). In TMT positive cases 75% were hypertensive and in TMT negative cases 44.6% were hypertensive, showing significant data (P< 0.05). 82.2% cases were dyslipidemic in TMT positive and 57.4% in TMT negative cases, showing statistically significant data (P< 0.05). 28.5% TMT positive cases and 42.5% TMT negative cases were habitual to do exercise in form of morning walk and jogging, but data is not statistically significant (P>0.05).

**Discussion**

Our study consisted of 75 known type-2 diabetics of variable disease duration without prior documented evidence of CAD, 28 (37.3%) patients were reported TMT positive, while 47 (62.7%) patients were reported negative. Prevalence of inducible ischaemia increases with age (P value 0.0032) and maximum at 51-60 years age group (60.8%). G. Premalatha et al also found that frequency of TMT positivity increased for every age interval until by the age group of 60 years and above. Gender wise TMT positivity in males is 40%, 50% and 50% and in females is 30%, 18.1% and 22.2% in group 1, 2 and 3 respectively showing higher prevalence of inducible ischaemia in male with p-value 0.0042 (significant).

G. Premalatha et al found higher prevalence among males, that failed to reach statistical significance concluded that IHD is as common in female as in male diabetics. In our study more positivity of IHD and may be unnecessarily subjected to further sophisticated invasive and noninvasive expensive investigations.

Silent ischaemia is defined as a definitely positive stress test in the absence of any symptoms such as angina or breathlessness (angina equivalent). Koistinen MJ had shown higher prevalence of SMI in diabetics as compared to non diabetics. In our study asymptomatic despite a positive
TMT (silent ischaemia) in group-1, 2 and 3 were 44.5%, 33.3% and 40% respectively. This shows that silent ischaemia is indeed a feature of NIDDM patients that can be easily detected by TMT. Prevalence of SMI on Stress Test in various studies done previously by Motoji N was 31%, Gupta SB and Pandit RB found 38.3%, Ahluwalia G et al reported 50%, Gibbons LW et al demonstrated 46.7%, Wackers FW et al found 22%, Misad group demonstrated that 12.1% of diabetics without prior coronary artery disease had SMI on TMT. This variable prevalence of SMI in different study groups could be explained with the involvement of number of vessels and degree of stenosis. Ahluwalia G et al concluded prevalence of SMI was 64% with 3-vessel disease, 50% with 2-vessel disease and 20% with 1-vessel disease and is higher with severe degree of CAD. Cardiac autonomic neuropathy seems to be the most probable reason for absence of pain for SMI.

In our study 34 cases had abnormal ECG at rest in form of ST-T changes out of which 13 (38.23%) were TMT positive where as 41 cases had normal ECG at rest out of which 15 (35.6%) were TMT positive with the Odds ratio 1.07 showing that TMT positivity in patients is more likely to occur in cases with abnormal resting ECG than with normal resting ECG. Study by MiSAD group et al concluded that abnormalities in ECG at rest had the highest odds ratio (9.27) for TMT positivity and ST-T abnormalities in ECG at rest is an important predicting factor for silent CAD in DM-2 patients and suggests an indication of performance of further investigations in presence of these abnormalities.

Association of Various Risk Factors with Result of TMT in Diabetics

There is a strong association between smoking and inducible ischaemia in our study as in TMT positive cases 67.8% were smoker with p-value 0.00000062. Alcohol intake is also a strong risk factor as 78.5% were alcoholic in TMT positive group compared to 27.8% alcoholic in TMT negative cases (p value 0.0004). Analysing BMI and TMT positivity, concludes that higher value of BMI (≥30) may be a significant contributory risk factor (P value 0.0318) in the development of CAD in diabetic cases. In TMT positive and negative group associated hypertension was present in 75% and 44.6% respectively (p-value 0.0105). Samuel Bellet et al demonstrated higher incidence of positive TMT in hypertensive diabetic subjects. We found strong correlation between microalbuminuria and silent ischaemia in diabetic patients as 57.1% cases showing microalbuminuria were positive for TMT where as only 14.9% cases had shown negative TMT (p value = 0.00007). Chico A, Thomas A, Novials A also concluded that inducible ischemia is associated with microalbuminuria and diabetic patients aged over 60 years should be screened for it specially if they have gradually increasing microalbuminuria. In our study macroalbuminuria also showed significant association (p = 0.021) with TMT positive cases (28.5%). Conclusion by Consensus development conference (1998) and Anurag S Lavekar et al suggest micro and macroalbuminuria are the proven risk factors for CAD in type 2 DM patients. Lipid abnormalities are very common in type 2 diabetes and it has great influence on coronary artery disease. In our study 82.2% cases are dyslipidemic in TMT positive and 57.4% in TMT negative cases, demonstrating statistically significant data, p-value 0.0274. Individual risk factors has shown VLDL to be very significant, triglyceride, Cholesterol and LDL to be significant where as HDL was not significant. SAMUEL BELLET et al also found increased cholesterol in diabetic TMT positive cases. Proportion of persons following exercising performance having negative TMT is higher than TMT positive group but is not statistically significant.

Disease Duration of Type-2 Diabetes Mellitus and Silent Myocardial Ischaemia

The average duration of DM-2 in all TMT positive cases was 4.91±2.51 years and in TMT negative cases was 3.59±2.13 years, which is highly significant (p-value =0.0095). According to our study greater is the duration of DM-2 chances of inducible ischaemia increases progressively but duration of diabetes is not a proven risk factor for silent ischaemia according to ADA. However, study by Langer A et al reporting positive correlation between the two. Study by Mee Kyoung Kim et al also recommends screening for CAD in elderly geriatric patients by TMT with a duration of diabetes ≥10 years.

There was no instance of TMT induced myocardial infarction or death in our study.

Undoubtedly, tools such as coronary angiography is more reliable in detection of ischaemia with good accuracy but TMT as a screening method can be an effective means of diagnosis of asymptomatic CAD in type-2 DM patients in areas where angiography is not easily available.

Conclusions

TMT in diabetic patients has a significant role in detection of silent myocardial ischaemia. Prevalence of silent myocardial ischaemia in DM-2 patients is 37.3%. There is significant correlation between risk factors of CVD and evidence of ischaemia on TMT in diabetic patients. Duration of diabetic state has a strong correlation for coronary inducible ischaemia on TMT. It may be a safer, cheaper, reliable and easily available non-invasive screening tool for earlier detection of CAD in diabetic patients.
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