

# A Prospective Study of Tread Mill Test in Postmenopausal Women

Sutakshee Sonwani<sup>1</sup>, Ram Awatar Rawat<sup>2</sup>, Puneet Rastogi<sup>3</sup>, O P Jatav<sup>4</sup>

## ABSTRACT

**Introduction:** Cardiovascular disease (CVD) accounts for 45% mortality in women. In post menopausal women risk factors like hypertension, dyslipidemia, obesity and diabetes are increasing. Cardiovascular risk assessment should be done at time of menopause and at regular intervals to detect cardiovascular disorders at the earliest. Current research aimed to study symptomatology and biochemical parameter and its relationship with ECG and TMT in postmenopausal women.

**Material and Methods:** Ninety postmenopausal women (40-50 years) were studied between January 2016 to September 2017 at Department of Medicine, J.A. Group of Hospitals, G.R. Medical College, and Gwalior. Patients were randomly divided as Cases (n=60; patients having at least one risk factor for CAD) and Control (n=30; patients with no risk factor for CAD). Postmenopausal symptoms, age, blood sugar, HbA1C and ECG were done in all patients. Treadmill test, ECG, TSH and urine for microalbuminuria were performed in all subjects. Data were analyzed using IBM SPSS ver. 20 software. P value of <0.05 is considered as significant.

**Results:** Mean age at menopause was 46.7 years, mean duration since menopause was 4.6 years, most of the subjects were illiterate (84%), had sedentary life style (88%) and were vegetarian (76%). Most common post menopausal symptoms were weakness/lethargy(60%), adverse mood (21.66%) and sleep disturbance (16.66%). Among cases and control, 9 and 1 patients was TMT positive (p<0.001). TMT was positive in one patient with night sweat (n=3), 5 patients with hot flashes (n=14), 2 patients with weight gain (n=4) and 1 patients with dyspareunia (n=2). Out of 9 TMT positive cases most of them were having BMI between 18.5-24.9 kg/m<sup>2</sup> (n=7), HbA1c <6.5% (n=7), total Cholesterol >200 mg/dl (n=5), Triglyceride >150 mg/dl (n=5), HDL <40 (n=7), LDL >130 (n=5), VLDL >30 (n=6) and TSH between 4.25 to 10 (n=3). TMT was also positive in one patient with LAE, 2 patients of low voltage complex, 5 patients with non specific ST-T changes and one patient with sinus bradycardia in ECG findings. Among risk factors TMT was positive in 6 patients with dyslipidemia, 2 patients with diabetes, 3 patients with hypothyroidism and 1 patient who was overweight.

**Conclusion:** TMT can help in early diagnosis and warrants further action and it is a good non-invasive screening tool for CAD in postmenopausal women. TMT is an important tool specially in postmenopausal women who are at 40-45 years of age to screen CAD.

**Keywords:** Postmenopausal Women, TMT, Lipid Profile, Diabetes, Menopausal Symptoms

United States statistics, accounted for 398086 female deaths in 2013.<sup>1</sup> In Indian population CAD is the leading cause of mortality and morbidity of both men and women accounting for over one third of total deaths. It has reached epidemic proportion among Indians. It accounts for 1 out of 3 women death regardless of the race or ethnicity.<sup>2</sup> In women, the annual mortality rate from CAD is high.<sup>3</sup>

Women who started menstruating at the age of 11 or younger, or entered menopause before 47, face a higher risk of heart disease and stroke. Estrogen helps protect women from heart disease before menopause. However, women with diabetes or abnormal lipids can still get heart disease before menopause. With decline in estrogen level, risk factor for coronary heart disease become more apparent. Risk factor identification is poorly managed in middle aged women and hence it should be the first step in evaluation and management of women of menopausal age.<sup>4,5</sup> Cardiovascular risk assessment should be done at time of menopause and at regular intervals to detect cardiovascular disorders at the earliest.<sup>6</sup>

Hence, the present study was planned to investigate importance of resting ECG findings and its relationship with stress ECG findings by TMT in postmenopausal women before the CAD becomes symptomatic as in developing countries diagnosis of risk factors of CAD is usually delayed.

## MATERIAL AND METHODS

A hospital based case control study was carried out in Department of Medicine, J.A. Group of Hospitals, G.R. Medical College, Gwalior (M.P), between January 2016 to September 2017, including 90 postmenopausal women (60 cases and 30 controls).

Women of age group between 40-50 years with diagnosis of menopause (>12 months amenorrhea / diagnosed by gynecologist) and with nonspecific symptoms were included. Women <40 years and >50 years of age, known case of coronary heart disease, hypertensive on drugs, women with surgical and medically induced menopause, osteoarthritis, low backache, women with known gynaecological disorders like malignancy, per vaginal bleeding etc. and any other

<sup>1</sup>PG 3rd Year Student, Department of Medicine, <sup>2</sup>Assistant Professor, Department of Cardiology, <sup>3</sup>Professor and HOD, Department of Cardiology, <sup>4</sup>Professor and HOD, Department of Medicine, GRMC Gwalior, India

**Corresponding author:** Dr. Ram Awatar Rawat, Assistant Professor, Department of Cardiology, GRMC Gwalior, India

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## INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in women and, according to the most recently released

condition that prevents them from doing TMT were excluded from the present study.

Approval from ethical committee and informed consent was taken from all enrolled patients after detailed counseling. The contents of the consent were read out to the patient in his/her language.

Complete blood count (CBC), serum creatinine, serum bilirubin, SGOT, SGPT, blood sugar, HbA1C and ECG was done in all patients. Treadmill test, echocardiography, TSH and urine for microalbuminuria were performed in all subjects. Thirty healthy post menopausal women who were not having any risk factors for CAD with age 40-50 years who had given informed consent were taken as control.

**Technique of treadmill test:** The patient was instructed not to eat or drink caffeinated beverages three hours prior to testing and to wear comfortable shoes and loose fitting clothes. A brief physical examination was performed prior to the test and a written informed consent was taken. A standard 12 lead electrocardiogram was taken following which a torso ECG was obtained in the supine position and in the sitting or standing position. Blood pressure was recorded in both positions and the patient was instructed on how to perform the test. Standard multistage maximal exercise test was done on a motorised treadmill according to Bruce protocol. The heart rate, blood pressure and electrocardiograms were recorded at the end of each stage of exercise, immediately before and after stopping the exercise and for each minute for at least 5 to 10 minutes in the recovery phase. Exercise test was terminated in all patients following the achievement of target heart rate or an abnormal ischemic response. This was defined as development of 0.10 mV (1 mm) of J point depression measured from the PQ junction, with a relatively flat ST segment slope (<1mV/sec), depressed > 0.10 mV 60 to 80 msec 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.

**STATISTICAL ANALYSIS**

All the data analysis was done using IBM SPSS ver. 20 software. Continuous data was presented as mean±SD. For calculation of significance between continuous variables between two proportions and percentages, Chi-square and Fischer’s test was used. P value of <0.05 is considered as significant.

**RESULTS**

Mean age at menopause was 46.7 years, mean duration since menopause was 4.6 years, most of the subjects were illiterate (84%), had sedentary life study (88%) and were vegetarian (76%).

In Cases (n=60) and Control group (n=30), 9 and 1 patients was TMT positive respectively (p<0.001). In women with night sweat (n=3) one, hot flashes (n=14) five, weight gain (n=4) two and with dyspareunia (n=2) one patient was TMT positive. In women with hot flashes (n=14) and weight gain (n=4), one in each had abnormal ECHO.

Among cases, 24 patients had family history out of that

7 had CAD, 7 had hypertension, 8 had diabetes, 1 had dyslipidemia and 1 had family history of obesity. Among cases, drug history was present in 26 patients whereas none of the patients in control had drug history. Among cases, most common ECG findings was non specific ST-T changes (n=8) followed by 5 patients who had VPC’S and 3 patients who had sinus bradycardia, among control most common ECG findings was T inversion (n=3) and VPC’S (n=3).

Most of the patients in cases (n=56) and control (n=30) had EF >55 (normal). In cases, 1 patient had mild systolic dysfunction and one had moderate systolic dysfunction. Most of the patients in cases (n=38) and control (n=30) had microalbuminuria (<30 mg/dl). Only 2 patients in cases had microalbuminuria between 30-300. Among cases, 24 patients were hypothyroid whereas among controls none of

Symptomatology	Female (N=60)	Percentage
Weakness/lethargy	36	60
Sleep disturbance	10	16.66
Adverse mood	13	21.66
Night sweat	6	10
Hot Flashes	14	23.33
Weight gain	6	10
Dyspareunia	3	5
Decreased appetite	6	10
Constipation	6	10

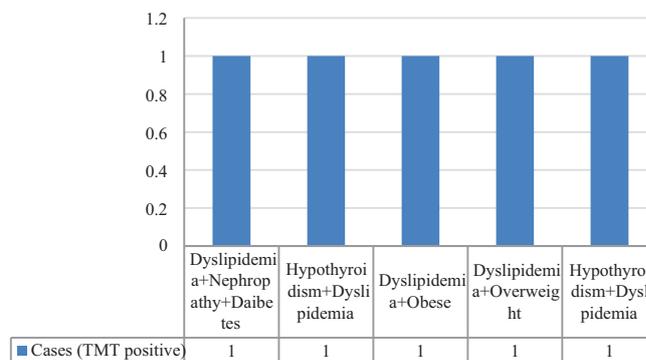
Data is expressed as no of patients and percentage

**Table-1:** Distribution of post menopausal symptoms among cases

TMT test parameters		Cases	Control
HR (beats/ min)	100-129	9	1
	130-159	49	29
	160-189	2	0
ST depression(mm)	<1	51	29
	1-2	5	0
	>2	4	1
Test induced angina	Yes	9	1
	No	51	29
Dukes score	≥5	51	29
	+ 4 to -10	9	1
	<-11	0	0

TMT; tread mill test, Hr; heart rate

**Table-2:** Distribution of tread mill test



**Graph-1:** Distribution based on risk factors (with two or more comorbidities)

Parameter		Cases		Control		P value
		TMT +ve	TMT -ve	TMT +ve	TMT -ve	
Age (years)	40-50	9	51	1	29	0.002
BMI (kg/m <sup>2</sup> )	18.5-24.9	7	32	1	29	0.002
	25-29.9	1	16	0	0	<0.001
	≥30	1	3	0	0	<0.001
HbA1c (%)	<6.5	7	41	1	29	<0.001
	6.5-8.4	1	4	0	0	<0.001
	≥8.5	1	6	0	0	<0.001
Lipids (mg/dl)	Total Cholesterol (>200)	5	26	0	0	<0.001
	Triglyceride (>150)	5	26	0	0	<0.001
	HDL(<40)	7	27	1	29	0.002
	LDL (>130)	6	40	0	0	<0.001
	VLDL (>30)	6	24	0	0	<0.001
ECG changes	Normal	0	29	0	18	0.002
	Early repolarisation	0	1	0	1	NS
	LAE	1	0	0	0	<0.001
	low voltage complex	2	5	0	0	<0.001
	RBBB	0	1	0	1	NS
	non specific ST-T changes	5	3	1	1	0.004
	Sinus bradycardia	1	2	0	0	<0.001
	Sinus tachycardia	0	2	0	2	NS
	T INVERSION	0	3	0	3	NS
	VPCS	0	5	0	3	0.023
Microalbuminuria	<30	0	50	0	0	NS
	30-300	1	1	0	0	NS
	>300	0	0	0	0	NS
TSH (μIU/ml)	4.25-10	3	21	0	0	<0.001
	11-50	0	0	0	0	NA
Risk factors	Family history of IHD	0	4	0	0	NA
	Smoking	0	0	0	0	NA
	Hyper-tension	0	1	0	0	NA
	Obesity	1	3	0	0	NA
	Dyslipidemia	6	25	0	0	NA
	Diabetes	2	10	0	0	NA
	Hypothyroid	3	21	0	0	NA
	Overweight	1	16	0	0	NA

Data is expressed as nu of patients, BMI; body mass index, TSH; thyroid stimulating hormone, ECG; electrocardiograph, HbA1c; glycated hemoglobin, TMT; tread mill test, NA; p value not available, NS; not significant. P value<0.05 is considered as significant.

**Table-3:** Comparing patient's distribution according to TMT status with different parameters between Cases and Control

the patients had hypothyroidism.

## DISCUSSION

Coronary artery disease (CAD) and peripheral vascular atherosclerosis is one of the most common causes of mortality in developing countries like India.<sup>7</sup> A recently observed and focused aspect of coronary artery disease is its silent and asymptomatic presentation. In postmenopausal women, there is a high risk of developing CAD and related disorders.

In present study, most common symptoms were weakness/lethargy (60%), hot flashes (23.33%) and altered mood (21.66). Singh et al studied 252 postmenopausal women and reported that the most common complaints of postmenopausal women were sleep disturbances (62.7%), muscle or joint pain (59.1%), hot flashes (46.4%) and night sweats (45.6%). Similar findings were reported by Madhukumar et al<sup>8</sup> and Nusrat et al.<sup>9</sup>

Study done by Nigam et al reported that the cases that had family history of CAD, hypertension or diabetes mellitus were highly susceptible for positive results of stress test (42.10%), which is comparable to the observation made in present study.<sup>10</sup>

Out of 12 diabetes patients in present study 2 were TMT positive, this is in accordance with Motoji et al who found 31% diabetics without prior evidence of coronary artery disease had treadmill test positive. Silent myocardial ischemia was 2.2 times more common in diabetics as compared to nondiabetics.<sup>11</sup> Another Indian study by Gupta et al reported 38.3% of diabetics without prior coronary artery disease had silent myocardial ischemia on exercise test.<sup>12</sup>

In present study, cases with BMI 18.5-24.9 (Normal), 25-29.9 (Over weight) and > 30 (Obese), 7, 1 and 1 were TMT positive respectively. In agreement to this Nigam et al<sup>10</sup> also reported that the cases having BMI >30 kg/m<sup>2</sup> had higher

incidence of positive stress test (40.00%). The findings of present study are in comparison with the observation of Framingham Heart study which had confirmed obesity as one of the independent risk factors in the genesis of coronary artery disease.<sup>13</sup> Gupta et al in 1995 studied 2212 adults of 20 years of more age, observed coronary risk factors in 11% of obese adults whose BMI was more or equal to 27 kg/m<sup>2</sup>.<sup>12</sup> Also the Ramchandran et al in 1998 by studying 953 subjects showed that the prevalence of obesity as a risk factor of CAD was more as compared to hypertension.<sup>14</sup> Sharda et al also reported that higher value of BMI ( $\geq 30$ ) may be a significant contributory risk factor (P value 0.0318) in the development of CAD in diabetic cases.<sup>15</sup>

In present study, 7 cases were TMT positive who had HbA1c level  $< 6.5$  whereas with HbA1c  $> 6.5$ , one patient was TMT +ve. Hyperglycemia and impaired glucose tolerance is a known risk factor which can directly lead to coronary heart disease. In agreement with present study Liu Yao et al concluded that HbA1c level is an independent predictor of total mortality in CAD patients without but not in patients with diabetes.<sup>16</sup>

Patients who had abnormal total Cholesterol ( $> 200$  mg/dl) five patients were TMT positive, had abnormal triglyceride ( $> 150$  mg/dl) five patients were TMT positive, had abnormal HDL ( $< 40$ ) seven patients were TMT positive and patients who had abnormal LDL ( $> 130$ ) five patients were TMT positive. A similar study done by Sharma et al reported that patients with subclinical hypothyroidism had significantly high serum hs-CRP, Lp (a), total cholesterol and LDL-C level as compared to control.<sup>17</sup> Roos et al had done bicycle ergometry and dobutamine stress echocardiography of 51 cardiac asymptomatic hypothyroid patients and found that HDL cholesterol was lower and triglyceride were higher but he did not get any positive result for bicycle ergometry.<sup>18</sup> According to Giral et al a positive exercise electrocardiogram is not infrequent occurrence in asymptomatic hypercholesterolemic patients, but the number of false positive tests may be relatively high (50%).<sup>19</sup>

TMT was also positive in one patient with LAE, 2 patients of low voltage complex, 5 patients with non specific ST-T changes and one patient with sinus bradycardia in ECG findings. 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 T2DM patients and suggests an indication of performance of further investigations in presence of these abnormalities.<sup>20</sup> Similar to present study Dhawale et al studied 100 patients without history of coronary artery disease and reported that most common abnormalities were bradycardia 10%, low voltage complex 7%, RBBB 7%, ST-T changes (nonspecific) 5% and VPC's 4%.<sup>21</sup>

A study done by Dhawale et al reported that out of 100 patients, TMT was positive in 12% of cases. Out of 12 TMT positive patients, serum TSH value  $> 10$  iU/ml was present in 11 (91%) of patients and only 1 (8.3%) had serum TSH values  $< 10$  iU/ml, in agreement with this in present study out

of 9 Cases who were TMT positive three patients had TSH between 4.25 to 10.<sup>21</sup>

Among the patients with dyslipidemia, 6 were TMT +ve, among diabetes 2 were TMT +ve, among Hypothyroid and overweight 3 and 1 patients was TMT +ve respectively. Sharda et al studied 75 T2DM cases who had undergone TMT procedure and reported that TMT positivity for inducible ischaemia in T2DM 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.<sup>17,20,23</sup> In agreement to Sharda et al, present study has shown that patients with risk factor such as diabetes, obesity, overweight, dyslipidemia and microalbuminuria are associated in TMT positive patients. Also situation become worse if the same patient is having multiple risk factors as in present study patients who were TMT positive, 1 had three risk factors together as Dyslipidemia + Nephropathy + Diabetes, 1 had Hypothyroidism + Dyslipidemia, 1 had Dyslipidemia + Overweight and one had Hypothyroidism + Dyslipidemia. Nigam et al reported that the patients having past history of hypertension with hypothyroidism had more positive stress test (33.33%) compared to normotensive (20%).<sup>10</sup> In present study, among the hypothyroid patients, 3 were TMT positive.

In present study, most of the patients in Cases (n=38) and Control (n=30) had normal microalbuminuria (mg/dL  $< 30$ ). Sharda et al found strong correlation between microalbuminuria and silent ischaemia as 57.1% cases showing microalbuminuria were positive for TMT where as only 14.9% cases had shown negative TMT (p value = 0.00007).<sup>15</sup> Chico et al 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.<sup>24</sup> In our study macroalbuminuria also showed significant association (p  $< 0.05$ ) with TMT positive cases.

Present study had few limitations; one being small sample size; a large clinical trial is needed to strengthen the present study findings.

## CONCLUSION

To conclude among postmenopausal women who were TMT positive, most of them had nonspecific symptoms with nonspecific ECG changes and abnormal lipid profile. About one third of postmenopausal syndrome had cardiovascular risk. Patients with abnormal lipid level should be tested for TMT parameters for early diagnosis of CAD. In most of the cases, diagnosis of CAD would have been missed if based on ECG and symptoms of the patient alone. Thus TMT helps in early diagnosis and warrants further action and it is a good non-invasive screening tool for CAD.

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