



# A STUDY OF SCREENING OF ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS PATIENTS BY TREADMILL TEST AND ITS CORRELATION WITH HIGH SENSITIVITY C-REACTIVE PROTEIN

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## ABSTRACT

**Background:** Progressive Coronary Artery Disease (CAD) remains asymptomatic in many cases of type 2 diabetes mellitus (T2DM) and this makes diagnosis difficult. The routine screening of T2DM for CAD using electrocardiography (ECG) is still debated due to the prevalence of normal ECG results in the majority of patients. Thus, the present study aims to study the screening of CAD on type 2 DM patients by Treadmill Test (TMT) and its correlation with high sensitivity C reactive protein.

**Materials and Method:** This observational study was carried out over one year in the Department of General Medicine at Dr. Balasaheb Vikhe Patil Rural Medical College, Loni involving 100 patients with T2DM. Detailed history of the patients were recorded, followed by clinical and biochemical tests. All patients underwent ECG and trans-thoracic echocardiography (ECHO). Those with normal ECG and ECHO results proceeded to an TMT. High Sensitivity C-reactive protein (HS-CRP) levels were measured in patients undergoing TMT using the immuno-turbidometric method.

**Result:** In the present study, 31% of patients tested positive on the TMT, with no significant age correlation ( $p=0.30$ ). Duration of diabetes also showed no significant correlation with TMT results ( $p=0.75$ ), though positive results were observed in 25.80% of patients with diabetes for <5 years, 54.84% for 5-10 years, and

19.35% for >10 years. Smoking showed a significant correlation with positive TMT results ( $p < 0.0001$ ), with 74.19% of positive results among smokers versus 14.49% among non-smokers. Additionally, the results represent a strong association between elevated HS-CRP levels and increased CAD risk.

**Conclusion:** The present study sheds light, on the fact that HS-CRP is an effective biomarker in the prognosis of challenging asymptomatic CAD. The early intervention of asymptomatic CAD in T2DM is crucial due to its high mortality and morbidity. Also, we highlighted that TMT is an effective tool for identifying primary CAD in patients with T2DM. We suggest that the introduction of medical intervention and regular physical exercise can reduce disease related morbidity and mortality.

**Keywords:** Coronary artery disease, Type 2 diabetes mellitus, Treadmill test, High Sensitivity C-reactive protein.

## INTRODUCTION

Coronary artery disease (CAD) is one of the major cardiovascular diseases (CVD) affecting the global human population. <sup>[1]</sup> Patients with diabetes mellitus (DM) are a high-risk group CAD because they more frequently develop CAD than non-DM patients and CAD progresses without symptoms and occasionally follows a serious clinical course. <sup>[2]</sup>

In adults with diabetes mellitus (DM), hypertension is prevalent in 75% to 85% of cases, elevated LDL in 70% to 80%, and obesity in 60% to 70%. CAD stands as the primary cause of mortality in both T1DM and T2DM, with DM linked to a 2 to 4-fold heightened risk of death from heart disease. Additionally, over 70% of individuals aged over 65 with DM will experience some manifestation of heart disease or stroke. <sup>[3,4]</sup>

CAD often remains asymptomatic in patients until it manifests as a myocardial infarction or sudden cardiac death. Therefore, proper screening and diagnosis of CAD are crucial for the prevention and early treatment of coronary events. Advances in technology and the clinical application of cardiovascular screening methods have significantly progressed in recent years. These modalities range from invasive procedures such as coronary arteriography to noninvasive tests like electrocardiograms, echocardiography, treadmill testing (TMT), coronary computed tomography (CT) angiography, and radionuclide studies. <sup>[5]</sup>

Additionally, Exercise TMT is a cost-effective, well-validated method for evaluating patients with suspected CAD. Besides detecting exercise-induced ECG changes indicative of ischemia, TMT provides crucial data on exercise capacity, blood pressure, and heart rate response to exercise, symptoms, and exercise-induced arrhythmias. For patients capable of exercising, this information can be utilized to assess both short- and long-term risks of mortality and cardiovascular events. <sup>[6]</sup>

Substantial evidence indicates a strong link between cardiovascular conditions and inflammation. Inflammation plays a crucial role in the pathogenesis of atherosclerosis, which can eventually lead to acute cardiovascular

events. Numerous large prospective trials have demonstrated that high reactive C reactive protein (HS CRP), an inflammatory biomarker, is an independent predictor of future cardiovascular events. <sup>[7]</sup>

Furthermore, a literature gap has been identified in this area. However, there is a need of further investigation. To address this gap, the present study aims to explore the screening of asymptomatic CAD in patients with T2DM using a TMT, and to examine its correlation with HS CRP levels.

## MATERIALS AND METHOD

The present study was observational study, conducted over one year in the Department of General Medicine at Dr. Balasaheb Vikhe Patil Rural Medical College, Loni. The present included 100 patients fulfilling the inclusion and exclusion criteria.

### Inclusion Criteria:

- All Type 2 Diabetes patients as defined by ADA.
- Age >40 yrs.
- Duration of Diabetes >5yrs.
- Family history of CAD.
- Hypertension.
- Dyslipidemia.
- Current Tobacco smoking.
- BMI >23 kg/m<sup>2</sup>
- hsCRP levels.
- Patients with normal ECG and Echocardiogram.

### Exclusion Criteria:

- Previous history of CAD/undergone coronary intervention.
- Patients with abnormal ECG and Echocardiogram suggestive of ischemia.
- Patient Refusal to give consent.
- Recently discovered Diabetes and type 1 diabetes.
- Severe valvular heart disease.
- Patients with chronic inflammatory condition.

**Methodology:**

Detailed history related to the present as well as a thorough history pertaining to other diseases was taken. Each patient was enquired about previous drug history, coronary artery disease, hypertension, diabetes and any other comorbid conditions. A thorough clinical test and biochemical investigations were done to categorise the patients into diabetic with asymptomatic and associated risk factors for coronary artery disease. An Electrocardiography was recorded for all patients and they were subjected to Trans thoracic Echocardiography. Patients with with normal ECG and ECHO will be undergoing to exercise treadmill test (TMT).

**HIGH SENSITIVITY C-REACTIVE PROTEIN**

Levels of High Sensitivity C-reactive protein will be measured in all patients who are subjected to tread mill testing by immuno turbidometric method.

**RESULTS:****Table-1:- Correlation of positive and negative TMT with age group**

Age group	Positive	Negative	Total	P-value
40- 50	9 (29.03%)	20 (28.99%)	29 (29.00%)	0.30
51 - 60	14 (45.16%)	37 (53.62%)	51 (51.00%)	
> 60	8 (25.81%)	12 (17.39%)	20 (20.00%)	
Total	31 (31.00%)	69 (69.00%)	100 (100.00%)	

In the study, positive TMT results were found in 29.03% of patients aged 40-50, 45.16% of those aged 51-60, and 25.81% of those over 60. Overall, 31% tested positive and 69% tested negative, with no significant correlation between age and TMT results (p-value 0.30).

**Table-2:- Correlation of positive and negative TMT with gender**

Gender	Positive	Negative	Total	P value
Male	25 (80.65%)	47 (68.12%)	72 (72.00%)	0.009
Female	6 (19.35%)	22 (31.88%)	28 (28.00%)	
Total	31 (100.00%)	69 (100.00%)	100 (100.00%)	

In the study, 31% had positive TMT results, with 29.03% aged 40-50, 45.16% aged 51-60, and 25.81% over 60, showing no significant age correlation (p-value 0.30).

**Table-3:- Correlation of positive and negative TMT with duration of diabetes**

Duration of DM	Positive	Negative	Total	P-value
< 5	8 (25.80%)	16 (23.19%)	24 (24.00%)	0.75
5-10	17 (54.84%)	40 (57.97%)	57 (57.00%)	
> 10	6 (19.35%)	13 (18.84%)	19 (19.00%)	
Total	31 (31.005)	69 (69.00%)	100 (100.00%)	

In the study, positive TMT results correlated with diabetes duration as follows: 25.80% for <5 years, 54.84% for 5-10 years, and 19.35% for >10 years. Overall, 31% tested positive and 69% tested negative, with no significant correlation (p-value 0.75).

**Table-4:- Correlation of hypertension with gender**

Hypertension	Yes	No	Total	P-value
Male	45 (69.23%)	27 (77.14%)	72 (72.00%)	0.40
Female	20 (30.77%)	8 (22.86%)	28 (28.00%)	
Total	65 (65.00%)	35 (35.00%)	100 (100.00%)	

In the study, hypertension was present in 69.23% of males and 30.77% of females. Among those without hypertension, 77.14% were male and 22.86% were female. Overall, 65% had hypertension and 35% did not, with no significant gender correlation (p-value 0.40).

**Table-5:- Correlation of positive and negative TMT with hypertension**

Hypertension	Positive	Negative	Total	P-value
Yes	29 (93.55%)	13 (18.84%)	42 (42.00%)	<0.0001
No	2 (6.45%)	56 (81.16%)	58 (58.00%)	
Total	31 (31.00%)	69 (69.00%)	100 (100.00%)	

In the study, 93.55% of positive TMT results were associated with hypertension, while 18.84% with negative TMT. Conversely, 6.45% of positive TMT results and 81.16% of negative TMT results were found. Overall, 31% tested positive and 69% tested negative for TMT, with a significant correlation between TMT results and hypertension (p-value < 0.0001).

**Table-6:- Correlation of positive and negative TMT with smoker**

Smokers	Positive	Negative	Total	P-value
Yes	13 (74.19%)	10 (14.49%)	33 (33.00%)	<0.0001
No	8 (25.81%)	59 (85.51%)	67 (67.00%)	
Total	31(31.00%)	69 (69.005)	100 (100.00%)	

In the study, 74.19% of positive TMT results were among smokers, compared to only 14.49% of negative TMT results. Conversely, 25.81% of positive TMT results and 85.51% of negative TMT results were among non-smokers. This indicated a significant correlation between smoking and positive TMT results, with a  $p < 0.0001$ .

**Table-7:- Correlation of smoking with gender**

Smoking	YES	NO	Total	P-value
Male	40 (100.00%)	32 (53.33%)	72 (72.00%)	
Female	0 (0.00%)	28 (46.67%)	28 (28.00%)	
Total	40 (40.00%)	60 (60.00%)	100 (100.00%)	

In the study, all smokers were male, constituting 100% of the male participants, while none of the female participants smoked. Among males, 53.33% were non-smokers, and among females, 46.67% were non-smokers. Overall, 40% of participants smoked, with a significant correlation between smoking and gender ( $p$ -value  $< 0.0001$ ).

**Table-8:- Distribution HSCRP mean vs CAD risk among study population**

HS-CRP	HSCRP<3 (N)	HSCRP>3 (N)	Mean $\pm$ SD	P-Value
Positive	2 (2.00%)	29 (29.00%)	4.71 $\pm$ 1.21	<0.0001
Negative	69 (69.00%)	0 (0.00%)	1.72 $\pm$ 0.15	

Individuals with HS-CRP levels above 3 mg/L had a significantly higher CAD risk (29%) compared to those with levels below 3 mg/L (2%). The mean HS-CRP level was markedly elevated in CAD-positive individuals (4.71  $\pm$  1.21 mg/L) compared to CAD-negative individuals (1.72  $\pm$  0.15 mg/L), with a  $p$ -value of less than 0.0001, indicating a strong association between elevated HS-CRP levels and CAD risk.

## DISCUSSION:

In the present study, CAD in patients with T2DM was assessed using the TMT. The study also emphasized the correlation between CAD and HS-CRP. Prior research has identified a literature gap regarding the absence of studies examining both the screening and correlation of CAD with HS CRP. Therefore, the current study aims to address this gap by focusing on the screening of CAD using the treadmill test and its correlation with HS CRP levels.

CAD is more prevalent in individuals with diabetes compared to non-diabetics. Diabetic patients may have advanced CAD while remaining asymptomatic. Treadmill testing is a valuable procedure for diagnosing asymptomatic CAD, particularly in diabetic patients.

In the present study, positive TMT results were found in 29.03% of patients aged 40-50, 45.16% of those aged 51-60, and 25.81% of those over 60. Overall, 31% tested positive and 69% tested negative, with no significant correlation between age and TMT results (p-value 0.30).

Additionally, in this study, hypertension was observed 69.23% of males and 30.77% of females. Additionally, the present study also indicated a significant correlation between smoking and positive TMT results, with a  $p < 0.0001$ . It was found that, 100% smokers were males while none of the female participants smoked.

Similarly, **Khanal et al.**,<sup>[8]</sup> conducted a study revealing that within the study population, hypertension was present in 78.6%, dyslipidemia in 64.3%, a family history of CAD in 11.9%, and smoking in 34.5%, among various traditional risk factors.

Mean duration of diabetes was  $9.3 \pm 3.2$  years with mean HbA1c of  $7.98 \pm 1.18$  %. Similarly, in the study conducted by **Khanal et al.**, 39 men and 45 women with a mean age of  $57.7 \pm 8.2$  years was found. This study also reported that, among various traditional risk factors, hypertension was present in 78.6% of the study population, dyslipidemia in 64.3%, family history of CAD in 11.9% and smoking in 34.5%.

In the current analysis, out of 100 patients 24 patients were 5 yrs or less than 5 years duration of diabetes, 57 patients were 5-10 years of duration of diabetes and 19 patients were >10 years duration of diabetes. Number of positivity is high among the group between 5-10 years duration of diabetes. **Kim et al.**,<sup>[9]</sup> have conducted the same study based on parameter of duration of diabetes with 213 patients. They found that patients with more than 10 years of duration of diabetes are having significant correlation of CAD. These results showed variation with the present study.

In the current analysis, it was observed that individuals with HS-CRP levels above 3 mg/L had a significantly higher risk of CAD. The study findings indicates a strong association between elevated HS-CRP levels and increased CAD risk, with a p-value of less than 0.0001.

A study conducted by **Cushman et al.**,<sup>[10]</sup> and **Al-Tu'maa et al.**,<sup>[11]</sup> demonstrated the correlation between increased HS-CRP and CAD. They also reported a significant effect of HS-CRP measurement on coronary heart disease risk. Similar study was conducted by **Zhou et al.**,<sup>[12]</sup> which reported that the level of HS CRP in asymptomatic patients with CAD was found to be relatively higher.

Hence this study concludes that levels of HS CRP is elevated in type 2 diabetes patients with underlying CAD even though they are clinically asymptomatic and this can be used as supportive marker for detection of underlying CAD in patients with T2DM. Additionally, treadmill testing was found to be the effective in the screening of CAD.

Furthermore, limited availability of data pertaining to traditional cardiovascular risk factors, such as smoking, family history, and hypertension, was observed in our study. Therefore, there is a need for further research to comprehensively assess the efficacy of routine screening for asymptomatic CAD within this particular patient subgroup.

## CONCLUSION:

The early identification of asymptomatic CAD in individuals with T2DM is of paramount importance, since CAD's responsible for mortality and morbidity rates. Treadmill testing emerges as a significant tool for detecting primary CAD, supported by levels of HS-CRP, serving as a surrogate marker. Timely initiation of medical interventions can significantly decrease disease-related morbidity and mortality rates. Controlling hypertension, smoking, maintaining strict blood sugar control, and avoiding physical inactivity can lower the risk of CAD. The present study has also highlighted a positive association between HS-CRP levels and the risk of CAD. However, further investigation is needed to elucidate the significance of these findings.

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