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Original Article

Effective Early Screening Modalities for Asymptomatic Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Coronary artery disease (CAD) is often asymptomatic in type 2 diabetes mellitus (DM) patients until the onset of myocardial infarction (MI) or sudden cardiac death. The aim of this study was to evaluate the effective early screening modalities for asymptomatic CAD in patients with DM at a tertiary care hospital. **Methods and Materials:** Patients aged ≥ 40 years with DM of at least 5 years duration were included in the study. Patients underwent all routine investigations to detect additional risk factors of diabetes followed by sequential screening using echocardiography (echo), treadmill exercise ECG or NH3-stress PET. **Results:** There were 39 men and 45 women with a mean age of 57.7 ± 8.2 years. The mean duration of diabetes was 9.3 ± 3.2 years and the mean HbA1c level was 7.98 ± 1.18 %. The sensitivity and specificity of echo was 15.4% and 94.4% respectively. Treadmill exercise ECG had a sensitivity of 73% and specificity of 35.3%. For NH3-stress PET with reversible perfusion defect (RPD) > 10%, the sensitivity and specificity of finding significant lesion on coronary angiography (CAG) was 100% and 83.3% respectively. Among various traditional risk factors for developing CAD, there was a strong statistical significance with hypertension, dyslipidemia and albuminuria ($p < 0.05$). **Conclusion:** Early screening for asymptomatic CAD among patients with DM is recommended especially for those who have DM of at least 5 years duration or have additional risk factors. Considering the cost and availability, treadmill exercise ECG should be considered as initial screening test followed by stratification with Duke Treadmill Score (DTS).

Key words: Type 2 diabetes mellitus, CAD, Treadmill exercise ECG, NH3-stress PET, Coronary angiography.

Key Messages: Early screening for asymptomatic CAD among patients with DM is recommended especially for those who have diabetes for more than 5 years or have additional risk factors like hypertension, smoking and dyslipidemia. Treadmill exercise ECG should be considered as initial screening test followed by stratification with DTS.

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INTRODUCTION

Coronary artery disease (CAD) is often asymptomatic in patients with type 2 diabetes mellitus (DM) until the onset of myocardial infarction (MI) or sudden cardiac death.[1] CAD is often more aggressive in patients with DM along with a higher complication rates as compared to their non-diabetic counterparts. Patients of DM who do not have other risk factors for CAD have 2-4 times higher risk of death for age matched controls. CAD in DM patients is particularly asymptomatic and is more likely to be without chest pain during unstable angina or myocardial infarction. This leads to delay in presentation to health service as well as delayed diagnosis. Occult CAD ranges from 20% to ≥50% in asymptomatic DM patients.[2-3] Autopsy findings have revealed that at least 3/4 of DM patients without overt clinical CAD have significant atherosclerosis.[4] It is of utmost importance to screen DM patients for CAD, however, regular clinical examination and ECG is not sufficient as many patients will have normal ECG at rest.[5] Hence, there is a need for more advanced, sophisticated and sensitive tests like stress SPECT/PET for early screening of CAD in asymptomatic DM patients.

The primary objective of this study was to evaluate the effective early screening modalities for asymptomatic CAD in patients with DM at a tertiary care hospital. The secondary objectives were to evaluate the association of cardiovascular risk factors (smoking, hypertension, obesity, dyslipidemia, family history of CAD) as well as to correlate the findings of echo, treadmill exercise ECG and stress PET in asymptomatic DM patients with coronary angiogram.

MATERIALS AND METHODS

Patients aged ≥ 40 years with DM of at least 5 years duration were screened for the study. Patients were excluded if they had history of clinical symptoms of typical angina or chest pain or have been previously diagnosed or treated for non-CAD heart disease such as inherited cardiac disorder, cardiac valve disease, heart failure, or arrhythmia. A detailed clinical history was collected and eligible patients underwent general physical examination, systemic examination, fundus examination and laboratory investigations including ECG, Hb level, HBA_1C, renal function tests, lipid profile, and 24 h urine protein. Echo was performed in all the eligible patients and if echo was normal, patients were asked to undergo a treadmill exercise ECG and to a further NH3-stress PET if treadmill exercise ECG was negative. Patients who were detected to have underlying CAD such as regional wall motion abnormalities (RWMA) on echo or positive test on treadmill exercise ECG or having RPD on NH3-stress PET, underwent coronary angiography. Significant CAD was defined as coronary artery luminal stenosis of > 50%. The study was conducted according to the ethical principles stated in the latest version of Helsinki Declaration, and the applicable guidelines for good clinical practice (GCP).

Statistical Analysis

Categorical data (variables including gender, hypertension, smoking, family history of CAD, dyslipidemia) was presented in the form of number and percentage. Quantitative data was represented in the form of mean ± SD or median in interquartile range as per the requirement. Normality of data was checked by measures of Kolmogorov Sminov test of normality.

Relationship between treadmill exercise ECG and stress PET with CAG was determined using kappa test along with the calculation of sensitivity, specificity and PPV. Chi-square test or Fisher`s exact test as appropriate was applied to see the associated between cardiovascular risk factors with CAD. The width of the resultant confidence intervals (CI) for parameters to be estimated was constructed with a significance level of 0.05, i.e., a 95% CI. Statistical analysis was conducted using IBM SPSS statistics (version 23.0).

RESULTS

A total of 150 diabetic patients were screened for the study and 98 were eligible for further testing. 84 patients consented for non-invasive testing by echo and treadmill exercise ECG. There were 39 men and 45 women with a mean age of 57.7 ± 8.2 years. The mean duration of diabetes was 9.3 ± 3.2 years and the mean HbA1c level was 7.98 ± 1.18 %. Main baseline patient characteristics are enumerated in Table 1 and the study flowchart is presented in Figure 1.

Evidence of RWMA was present in 3 (3.6%) patients whereas the same was normal in 81 (96.4%) patients. Of the 81 patients who were normal on echo, 78 underwent treadmill exercise ECG whereas the same could not be performed in 3 patients due to diabetic foot or osteoarthritis knee. Of the 62 patients who were eligible for stress PET (59 patients who had no inducible ischemia on treadmill exercise ECG and 3 patients where treadmill exercise ECG could not be performed), 44 (71%) patients consented for stress PET. In these 44 patients, 22 (50%) had RPD while the other 50% patients had no RPD (Table 2).

Overall out of the 84 patients, 22 (26.2%) had either echo or treadmill exercise ECG abnormality and consented for CAG. 44 (71%) out of remaining 62 patients who did not have echo or treadmill exercise ECG abnormality, further consented for stress PET. Of these 44 patients, 22 (50%) had RPD and 9 (40.9%) out of these 22 patients further consented for CAG. In all, 31 patients underwent CAG. Prevalence of CAD was

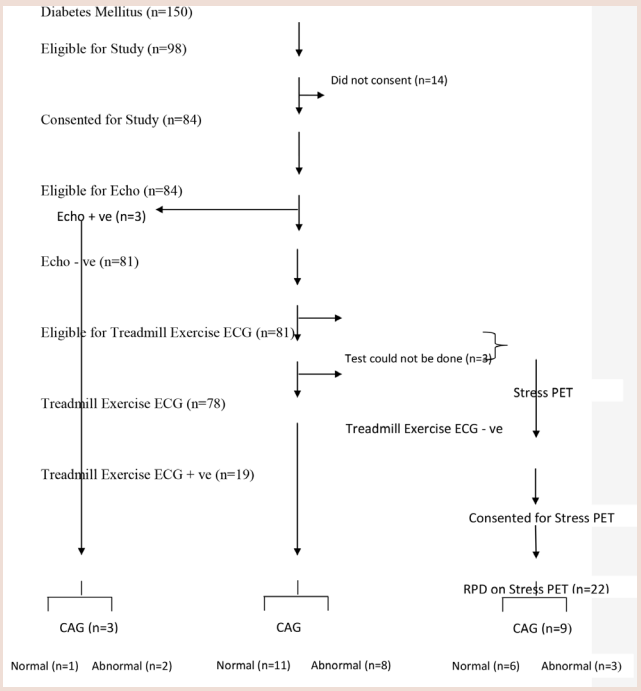

Figure 1: Study Flowchart.

Table 1: Baseline Patient Characteristics.

Enrolled	84
Gender, n (%)	
Male	39 (46.4)
Female	45 (53.6)
Mean Age (years)	57.7±8.2
Mean Duration of Diabetes (years)	9.3±3.2
Mean HbA1c level (%)	7.98±1.18
Hypertension, n (%)	66 (78.6)
Smoker, n (%)	29 (34.5)
Family History of CAD, n (%)	10 (11.9)
Dyslipidemia, n (%)	54 (64.3)
Diabetic Retinopathy, n (%)	29 (34.5)
Albuminuria, n (%)	33 (39.3)
Diabetic Neuropathy, n (%)	33 (39.3)

Table 2: Prevalence of CAD (Echo, Treadmill Exercise ECG and Stress PET Results).

Modality	Number of Patients (n)	Positive	Negative
Echo	84	3	81
Treadmill exercise ECG	78	19	59
Stress PET	44	22	22

Table 3: CAG *vis-a-vis* Echo, Treadmill Exercise ECG and Stress PET.

Modality	Normal n (%)	CAG Abnormal n (%)	
ECHO		1 (5.6%)	2 (15.4%)
Treadmill Exercise ECG	Low	7 (38.9%)	2 (15.4%)
	Medium	4 (22.2%)	3 (23.1%)
	High	0	3 (23.1%)
Stress PET	<10% RPD	5 (27.8%)	0
	> 10% RPD	1(5.6%)	3 (23.1%)

Table 4: Treadmill Exercise ECG Subtype and Extent of Disease on CAG.

Treadmill Exercise ECG Subtype	CAG Subtype				
	Normal	SVD	DVD	TVD	Total
Low	7 (77.8%)	2 (22.2%)	0	0	9 (47.4%)
Medium	4(57.1%)	1(14.3%)	1(14.3%)	1(14.3%)	7(36.8%)
High	0	1(33.3%)	2 (66.7%)	0	3(15.8%)
Total	11(57.9%)	4 (21%)	3 (15.7%)	1(5.2%)	19

Table 5: Population Characteristics and CAD.

Characteristics	CAD (mean ± SD)	No CAD (mean ± SD)	p value
Age	59 + 8.4	56.2 +7.9	0.113
Diabetic duration	9.4 + 3	9.2 + 3.3	0.844
HbA1c	8.1 +1.2	7.8 +1.2	0.339

11.9% by echo and treadmill exercise ECG and 19.7% by echo, treadmill exercise ECG and stress PET.

Table 3 presents the results of CAG vis-à-vis echo, treadmill exercise ECG and Stress PET. Of the 3 patients who had RWMA on echo, angiographically significant disease was found in 2 (66.7%) patients. While 1 patient had single vessel disease (SVD) the other patient had triple vessel disease (TVD). Of the 19 patients who had inducible ischemia on treadmill exercise ECG, angiographically significant disease was present in 8 (42.1%) patients. Of the 9 patients with RPD on stress PET, 5 (55.6%) patients with <10% RPD, had normal CAG with no significant lesion (p value=0.016). Of the 4 (44.4%) patients with > 10% RPD on stress PET, 1 (11.1%) patient had normal CAG whereas 3 (33.3%) patients had angiographic evidence of CAD (p value=0.016).

Table 4 presents the results of treadmill exercise ECG subtype and extent of disease on CAG. In the low risk category, 2 patients had SVD whereas remaining 7 patients had no angiographically significant lesion (p value =0.023). In the medium risk category, 3 patients had probability of angiographically significant lesion with 14.3% probability each for SVD, double vessel disease (DVD) and TVD lesion (*p* value=0.023). In the high risk category, all 3 patients had probability of angiographically significant lesion with probability of SVD being 33.3% and DVD 66.7% (*p* value=0.023). Overall, treadmill exercise ECG had a sensitivity of 73% and specificity of 35.3% with PPV of 42%.

Of the 3 patients who had > 10% RPD on stress PET with abnormal CAG, 1 patient had SVD while 2 patients had DVD. Therefore, for stress PET with RPD > 10% sensitivity and specificity are 100% and 83.3% respectively for finding significant lesion on CAG with PPV of 75%.

Of the 44 patients who had evidence of CAD by either echo or treadmill exercise ECG or stress PET, 31 patients consented for CAG and 13 patients had angiographic evidence of coronary artery disease. Table 5 presents the population characteristics of age, diabetic duration and HbA1c level in CAD vs. non-CAD subgroup of patients.

In our study a statistically significant association was found with hypertension, dyslipidemia and albuminuria. Hypertension was present in 62% of the patients who had CAD (p=0.01) whereas dyslipidemia and albuminuria was present in 64.8% (p=0.002) and 69.7% (p=0.011) patients respectively. In our study, the mean age of study population, duration of diabetes and HbA1c level were more in CAD group as compared to non CAD group however this was not statistically significant.

DISCUSSION

With epidemic of diabetes going uncontrolled worldwide including India, issues related to it are a need of immediate concern. DM is being considered as CAD equivalent, elevating it to the highest risk category level. Though the incidence of CAD has declined over time, DM is still continuing to be a significant risk factor.[6] Further, the incidence of asymptomatic CAD in diabetic population is posing a challenge for the overall management of the disease. The aim of this study was to evaluate the effective early screening modalities for asymptomatic CAD in patients with DM along with the assessment of risk factors and screening tests to be employed for the early diagnosis and management of the disease.

There were 39 men and 45 women with a mean age of 57.7 ± 8.2 years. Mean duration of diabetes was 9.3±3.2 years with mean HbA1c of 7.98±1.18 %. 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%. These characteristics are in concordance with findings of some of the previous studies.[7-9]

Prevalence of asymptomatic CAD in DM

In our study prevalence of asymptomatic CAD in the overall study population was 19.7% using a definition of luminal stenosis of > 50% on coronary angiography. The prevalence of asymptomatic CAD was only 11.9% when considered with treadmill exercise ECG alone but increased to 19.7% when considered with RPD of > 10% on NH3-Stress PET. This again reiterates the wide range of prevalence among various studies ranging from 11 to 60%.[9-22] The higher prevalence rates are due to studies which were retrospective in nature, studies with angiographic evidence of CAD,[23] studies which included patients with abnormal ECG and studies which used stress imaging.[24] Studies which showed low prevalence rates were those which were carried out in non-insulin dependent population, studies which excluded population with microvascular complications and those which used angiographic evidence for defining CAD.[11] Also higher prevalence after considering stress PET in present study could be due to the exclusion of population group which did not consent for stress PET following a negative result on treadmill exercise ECG.

Risk factors for CAD in DM

In our study statistically significant association was found with hypertension, dyslipidemia and albuminuria. Hypertension was present in 62% of those who had CAD (p=0.01) whereas dyslipidemia and albuminuria was present in 64.8% (p=0.002) and 69.7% (p=0.011) patients respectively. In a previous study by Yoo *et al*. statistical significance was seen with hypertension but not with dyslipidemia or albuminuria.[7] In a study by Gazzaruso *et al*. statistically significant association of CAD was found with dyslipidemia and microalbuminuria but not with hypertension.[8] However, Scognamiglio *et al*. reported a statistical significance with hypertension, dyslipidemia and microalbuminuria.[9] In this study statistical significance was also found with smoking, peripheral vascular disease and in those having a family history of CAD. This difference is likely due to the nature of present study which was done in smaller group of population and in older population with diabetes duration of more than 5 years. In our study statistical significance was not found with family history of CAD likely due to smaller study population and referral bias of being carried out at a tertiary care centre. In a nationwide survey of 6,032 women and 5,612 men with type 2 diabetic patients regularly attending diabetes clinics in Italy, the prevalence of microvascular complications (retinopathy, blindness, nephropathy, and foot ulcers) at baseline was found to be significantly higher among patients who developed coronary heart disease than among those who did not. The presence of microvascular complications enhanced risk by 35% in women and 20% in men. Correspondingly, incidence rates of all outcomes were higher in patients with rather than without microvascular complications. Therefore, early screening for asymptomatic CAD among patients with DM may also be considered after the emergence of microvascular lesions.[25]

In our study, the mean age of study population, duration of diabetes and HbA1c level were more in CAD group as compared to non CAD group; however this was not statistically significant. There are many previous studies which are consistent with these claims. In a retrospective population based cohort study in Canadians using provincial health claim database, transition to high risk category (10 years event risk of greater than 20%) occurred at younger age in diabetics.[26] In a prospective study of 5934 patients by Wannamethee *et al*. risk of CAD events increased with increasing duration of diabetes.[27] There is a graded risk for HbA1c level with any cardiovascular event as shown in meta-analysis of 13 prospective cohort studies which showed that for every 1% point increase, relative risk for cardiovascular event was 1.18 (95% CI of 1.10-1.26).[28] However, these characteristics were not statistically significant in our study due to

smaller study population as well as due to the inclusion criteria of > 40 years of age with duration of diabetes of more than 5 years.

Echo vs. Asymptomatic CAD and CAG

Echo as a first line investigation for detecting asymptomatic CAD is not a good choice as it is likely to have low sensitively. In our study, among 84 patients who underwent echo only 3 (3.6%) patients had RWMA. In the remaining 81 patients CAD was detected by either treadmill exercise ECG or stress PET in 13 patients. Further, out of 3 patients who had RWMA, 2 (66.67%) patients had significant lesion on coronary angiography with one having SVD and the other having TVD requiring revascularization therapy. One patient who didn`t show significant lesion on CAG had an ejection fraction of 25-30% apart from severe LAD territory hypokinesia. Echo also had specificity of 94.4% with significant lesion on CAG. Sensitivity and PPV were 15.4% and 66.7% respectively. Thus in view of very low sensitivity it should not be considered as first line investigation for screening. However in specific subgroup of population who cannot undergo treadmill exercise ECG, it may be considered as an option as the next battery of investigation as stress perfusion scans are costly with limited availability.

Treadmill exercise ECG *vs.* CAD and CAG

In our study, 81 patients were eligible for treadmill exercise ECG testing out of which 78 patients underwent treadmill exercise ECG and remaining 3 could not undergo this test due to coexisting diabetic foot or severe osteoarthritis of knee. Of the 78 patients, treadmill exercise ECG was positive in 19 (24.4%) patients. All 19 patients consented for CAG and significant lesion was found in 8 (42.1%) patients requiring revascularization therapy. Thus, prevalence of CAD in our study population was 10.3% when considered with treadmill exercise ECG alone. In a study by Yoo *et al.* prevalence of asymptomatic CAD was 29.8% by treadmill exercise ECG.[7] Sarkar *et al.* reported the prevalence of asymptomatic CAD in DM as 27.9%.[29] Thus prevalence of asymptomatic CAD in DM patients reported in our study is lower to the previous reports. Of the 19 patients who underwent CAG, stratification by DTS constituted low, medium and high risk groups as 47.4%, 36.8% and 15.8% respectively. Among low risk group 77.8% had no significant lesion on angiography (p=0.023) whereas in the high risk group all 3 patients had significant stenosis on angiography with one patients having SVD and other two having DVD (p=0.023). Thus, low risk stratified group on treadmill exercise ECG should not be advised for CAG unless there are additional risk factors for CAD. In medium risk group of 7 patients, 57% had normal CAG with 43% having significant lesion on CAG. Thus, in the patients with medium risk on DTS, option of diagnostic CAG should be recommended in those with additional risk factors for CAD. Patients in high risk group should strongly be recommended to undergo CAG to decide on revascularization therapy. Monitoring of carotid atherosclerosis and carotid plaque can also be considered as early screening tool for asymptomatic CAD among patients with DM. In a study by Wu Y *et al.* carotid atherosclerosis and its relationship to coronary heart disease and stroke risk in 1584 patients with type 2 diabetes mellitus was evaluated. Carotid atherosclerosis and carotid plaque were prevalent in patients with T2DM and positively correlated with 10-year coronary heart disease and stroke risk. Carotid atherosclerosis was found to be an independent risk factor for 10-year coronary heart disease risk.[30]

Stress PET *vs.* CAD and CAG

Of the 62 patients who were eligible for stress PET in our study, 44 (71%) patients consented for the test. In these 44 patients who were asymptomatic for CAD by echo and/or treadmill exercise ECG, 50% had RPD whereas 50% did not have any RPD. Of the 22 (50%) patients who had RPD, 11 patients (50%) had <10% RPD and remaining 11 patients had10% RPD. 9 (41%) out of these 22 patients consented for further evaluation by CAG. Among these 9 patients, 5 (55.6%) patients who had < 10% RPD on stress PET, did not have any significant lesion on coronary angiogram (p value=0.018). Of the remaining 4 (44.4%) patients with RPD of > 10 %, 3 (75%) had significant lesion on CAG (p value=0.018) with two patients having the DVD and the other one patient having a SVD. Thus, the prevalence of asymptomatic CAD upon addition of stress PET as screening modality in our study was 19.7%. Though, there are no studies which performed N13 ammonia stress PET dedicated to detect asymptomatic CAD in diabetes, there are few studies which studied the role of stress PET with rubidium or ammonia for detection of CAD and compared it with SPECT studies. Di Carli *et al.* reported a weighted sensitivity and specificity of PET/CT as 0.90 and 0.89 respectively among 9 studies including 877 patients.[31] In a study by Bateman *et al.* specificity was shown to be significantly higher with PET as compared to SPECT (93 vs. 73%), whereas sensitivity was only marginally increased (87 vs. 82%).[32] In various studies that used SPECT/stress echo for the detection of CAD in diabetic patients the prevalence varied from 44-60%.[11-12,15,24] Hence, the subgroup which had > 10% RPD is likely to have a significant lesion on CAG, which in the present study was 75% and should be recommend for CAG and revascularization therapy if indicated.

Thus, echo alone has a very low sensitivity of 15.4% to detect the asymptomatic CAD with a significant lesion on an angiogram. Treadmill exercise ECG has a sensitivity of 73% which is fairly acceptable but has a low specificity of 35.5%. Considering the cost and availability, treadmill exercise ECG can be considered as initial screening test in asymptomatic population of DM followed by stratification with DTS. Stress PET with a RPD of > 10% has sensitivity of 100% and specificity of 83.3% making it an ideal choice out of the three tests. However, the cost and availability of this test are major limitations for its adoption as an effective early screening modality for asymptomatic CAD in Patients with DM. Further, large studies to validate this claim along with the evaluation of health economics seem warranted.

CONCLUSION

Among various traditional risk factors for developing CAD, the present study showed strong statistical significance with hypertension, dyslipidemia and albuminuria (p value <0.05). Screening for asymptomatic CAD among diabetics is recommended especially among those who have diabetes for more than 5 years or have additional risk factors like hypertension, smoking, dyslipidemia, family history of CAD and micro or macrovascular complications of diabetes. Considering the cost and availability, treadmill exercise ECG should be considered as initial screening test in asymptomatic population of diabetics followed by stratification with DTS. The low risk group by treadmill exercise ECG should not be routinely advised for coronary angiogram. The medium risk group should be advised for further investigation by coronary angiogram only in the presence of additional risk factors for CAD. The high risk group should strongly be recommended for coronary angiogram and considered for revascularization therapy where indicated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CAD: Coronary Artery Disease; **DM:** Diabetes Mellitus; **MI:** Myocardial Infraction; **ECHO**: Echocardiography; **RPD:** Reversible Perfusion Defect; **CAG:** Coronary Angiography; **ECG:** Electrocardiography; **DTS:** Duke Treadmil Score; **SPECT:** Single Photon Emission Computed Tomography; **PET:** Positron Emission Tomography; **RWMA:** Regional Wall Motion Abnormalities; **GCP:** Good Clinical Practice; **SD:** Standard Deviation; **PPV:** Positive Prediction Value; **CI:** Confidence Interval; **SVD:** Single Vessel Disease; **DVD:** Double Vessel Disease; **TVD:** Triple Vessel Disease; **LAD:** Left Anterior Descending.

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