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Original Article

Assessment of asymptomatic ischemic heart disease using stress myocardial perfusion imaging in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Coronary artery disease (CAD) is the leading cause of death in patients with type 2 diabetes mellitus (T2DM) and may be asymptomatic.
Objective: The objective of this study was to assess the prevalence of asymptomatic myocardial ischemia in patients with T2DM using stress myocardial perfusion imaging.
Methods: We evaluated 97 consecutive patients with T2DM without clinical evidence of CAD presenting to Cardiology and Endocrinology clinics using **Tc-99m MIBI** gated single-photon emission–computed tomography (SPECT) myocardial perfusion imaging for the presence of asymptomatic CAD.
Results: Abnormal myocardial perfusion was observed in 10 patients (10.3%). Of these, one half of patients had reversible myocardial perfusion defects suggestive of inducible myocardial ischemia. The other half had fixed perfusion defects suggestive of previous silent myocardial infarctions. Small and moderate reversible perfusion defects were observed in 3 and 2 patients, respectively. The fixed perfusion defects observed in 5 patients were medium sized. The presence of asymptomatic ischemia was significantly associated with age and smoking but not with other traditional cardiac risk factors.
Conclusion: Ten percent of patients with T2DM with no clinical evidence of CAD were found to have evidence of asymptomatic ischemia or infarction.

1. Introduction

Type 2 diabetes mellitus (T2DM) confers an increased risk of development of coronary artery disease (CAD). The risk is two to four times greater in those with T2DM than those without and is especially high in diabetic women.[1] Cardiovascular diseases account for an overwhelming 65%–75% of deaths in people with diabetes mellitus (DM).[2,3] An additional feature of CAD in T2DM is that many individuals may have atypical symptoms or be totally asymptomatic, a condition referred to as silent or asymptomatic myocardial ischemia.

There is paucity of data regarding the prevalence of asymptomatic ischemia in Indian subjects although this issue is all the more relevant with regard to the Indian population due to the rising prevalence of DM, greater susceptibility to development of CAD, a tendency to underreport symptoms, and low physical activity levels. Our study was designed to estimate this prevalence.[4]

2. Methods

Ninety-seven consecutive patients were recruited from the Endocrinology and Cardiology outpatient clinics of AIIMS, New Delhi, a tertiary care hospital, from April 2015 to August 2016. The protocol procedures were approved by the Institutional Ethics Committee.

Inclusion criteria were T2DM (based on WHO criteria) with onset above the age ≥30 years and either (1) age ≥50 years or (2) age ≥45 years with at least one cardiovascular risk factor including

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(a) blood pressure >140/90 mmHg or on antihypertensive treatment, (b) dyslipidemia (total cholesterol ≥240 mg/dl, LDL cholesterol ≥130 mg/dl, or HDL cholesterol <35 mg/dl), (c) cigarette smoking, and (d) family history of premature CAD (defined as a first-degree male relative ≤55 years of age or a first-degree female relative ≤65 years of age).

Exclusion criterion included (1) the presence of angina pectoris or anginal equivalent symptoms, (2) a history of myocardial infarction, heart failure, or coronary revascularization, (3) electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST-segment or T-wave changes, or complete left bundle branch block, (4) stress test or coronary angiography during the 3 years before entry into the study, or (5) any clinical indication for stress testing.

After obtaining written informed consent, potentially eligible patients were screened for the presence of angina using the Rose questionnaire. A resting 12-lead electrocardiogram (ECG) was performed, and hemoglobin A_{1C} (HbA_{1C}) levels were measured. Anthropometric measurements were recorded.

2.1. Tc-99m MIBI gated myocardial perfusion SPECT

All patients underwent one-day low-dose stress (8–10 mCi)/high-dose rest (25–30 mCi) protocol, gated Technetium-99m Sestamibi (Tc-99m MIBI) myocardial perfusion single-photon emission–computed tomography (SPECT) imaging as per as the American Society of Nuclear Cardiology guidelines.[5] Stress exercise test on treadmill was conducted in accordance with the standard Bruce protocol. Twelve-lead ECG was monitored continuously. At peak exercise, patients were administered 8–10 mCi of Tc-99m MIBI intravenously, and exercise was continued for a minute.

The stress images were acquired about 30–45 min after the injection. In case the patient was unable to perform physical exercise, pharmacologic stress testing was performed with dobutamine intravenous infusion. Dobutamine was infused in stages of 3-min duration, with increasing doses of 10 μg/kg/min to a maximum of 40 μg/kg/min. Tc-99m MIBI was injected when target heart rate or standard end point was achieved. The rest images were acquired after intravenous administration of 24–30 mCi of Tc-99m-MIBI, 2–3 h after the stress study. Gated SPECT acquisition was performed on a SPECT/CT dual head gamma camera system.

2.2. Image processing

All studies were uniformly processed with commercially available Emory Cardiac Toolbox (ECTbox; Emory University, Atlanta, GA, USA) software on a Xeleris nuclear medicine workstation (GE Medical Systems; Waukesha, WI). SPECT projection images were reviewed in cine mode in all cases to assess patient movement, sources of potential attenuation artefacts, and gastric activity. Subsequently, tomographic slices were generated and displayed as short-axis and vertical and horizontal long-axis slices.

2.3. Image analysis

All SPECT images were analyzed according to the standard criteria by a nuclear medicine physician. The study was considered as normal (no perfusion defect on the stress and rest images) or abnormal (presence of perfusion defect on the stress). Perfusion defects on the stress images were described in terms of size, site, and severity. The defects were classified as fixed, reversible, or partially reversible defects, depending on the normalization of these defects on the corresponding rest images. Soft tissue attenuation correction algorithms were applied.

Reconstructed SPECT images were quantified using ECT box software and appropriate normal reference databases using the 20-segment model. The reconstructed short-axis slices were divided automatically into 18 radial sectors. The apex cap, derived from a segment of central horizontal long-axis slices, was divided into 2 sectors. The defects were subgrouped into anterior (anterior, anteroseptal, anterolateral, and apex) and inferior defects (inferior, inferoseptal, and inferolateral). By summation of all areas of the circumferential profiles below the normal limits and after adjustment for the varying volume of slices, the total defect size was calculated and expressed as a percentage of the left ventricle (LV). The perfusion defects were classified as small, medium, and large (<10%, 10–20%, and >20% of LV myocardium, respectively). The severity of perfusion defect was assessed on the percentage uptake in each segment compared with the segment with maximum uptake (more than 70%, normal; 50%–69%, mildly reduced; 30%–49%, moderately reduced; 10%–29%, severely reduced; and less than 10%, absent). Left ventricular ejection fraction was derived from the rest gated studies of all the patients using ECT box cardiac quantitative software.

2.4. Data analysis

Data are presented as mean ± standard deviation (SD) or median with lower and upper ends of the interquartile range. Multivariate associations were tested using *t* tests, Wilcoxon's rank-sum test, and Fisher's exact test.

3. Results

Ninety-seven consecutive patients with T2DM fulfilling the inclusion criteria were recruited. Baseline characteristics of the patients are shown in Table 1. Mean age of the patients was 53 years with range of 45–74 years. Sixty-five patients (67%) were male, and thirty-two patients (33%) were female. The mean duration of DM after diagnosis was 5.3 years with a range of 1–12 years. Seventy-two patients (74.2%) were hypertensive, and forty-three (44.3%) patients were on statins. Sixteen patients (16.5%) were current smokers, and seven (7.2%) had family history of premature CAD. Mean HbA_{1C} was 7.9%.

All patients underwent exercise stress testing except two in whom dobutamine stress testing was done. Sixty-five patients (67%) achieved target heart rate of 85% or more. Target heart rate was achieved in 80% of the patients with perfusion abnormalities.

Overall, 90% patients had normal perfusion test. Ten patients (10.3%) had abnormal myocardial perfusion suggestive of myocardial ischemia or infarction (Table 2). Five of these patients had reversible perfusion defects, suggestive of inducible myocardial ischemia. The perfusion defects in the remaining five patients were fixed, suggestive of previous myocardial infarction.

Small-sized reversible perfusion defects (involving <10% of LV myocardium) were observed in 3 patients (3.1%), and moderate-sized reversible perfusion defects (involving 10–20% of LV myocardium) were observed in 2 (2.1%). Transient ischemic dilatation was observed in both patients having moderate stress–induced ischemia. One of these patients had severe LV dysfunction at rest.

Fixed medium-sized perfusion defects were observed in 5 patients (5.2%). Four of these fixed defects involved the inferior wall, whereas one was anterior in location. One patient with fixed large perfusion defects had severe left ventricular dysfunction at rest. Lung uptake was observed in none of the patients.

In addition, one patient had mild left ventricular dysfunction with normal myocardial perfusion.

Abnormal myocardial perfusion was significantly associated with age and smoking. There was no significant association with

Table 1
Baseline patient characteristics.

Demographic characteristics	N (%)
Total number of patients screened	112
Number of patients excluded from the study	15
Number of patients included in the study	97
Men/women (%)	65 (67%)/32 (33%)
Age (years)	53.3 ± 8.3
Diabetes-related and cardiac risk factors	
Diabetes duration (years) (IQR)	5.3 (1–8)
HbA_{1c} (Mean) (%)	7.9 ± 1.6
<7%	14 (14.5)
7%–8%	50 (51.5)
>8%	33 (34.0)
BMI (kg/m^2)	25.5 ± 3.9
ADA consensus guidelines risk factors	
Lipid abnormality or lipid-lowering treatment (%)	50 (51.5)
Blood pressure >140/90 mmHg or hypertension treatment (%)	72 (74.2)
Smoking (%)	16 (16.5)
Family history of CAD (%)	07 (07.2)

IQR: interquartile range; BMI: body mass index; CAD: coronary artery disease; HbA1c: glycosylated hemoglobin; ADA: American Diabetes Association.

Table 2
SPECT results ($n = 97$).

Result	*n*	Percentage
Normal stress test	87	89.7
Abnormal myocardial perfusion	10	10.3
Reversibility	05	05.2
Mild stress–induced ischemia	03	03.1
Moderate stress–induced ischemia	02	02.1
Fixed perfusion defect size (percent of left ventricle)	05	05.2
Small (<10%)	00	00.0
Moderate (≥10 and < 20%)	02	02.1
Large (≥20%)	03	03.1
Anatomic location		
Anterior	02	02.1
Inferior	08	08.2
Other associated abnormality in patients with abnormal myocardial perfusion		
LV dysfunction	02	02.1
TID	02	02.1
TID and LV dysfunction	01	01.0
Normal myocardial perfusion	87	89.7
Other associated abnormality in patients with normal myocardial perfusion		
LV dysfunction	01	01.0
TID	00	00.0
TID and LV dysfunction	00	00.0

LV: left ventricular; TID: transient ischemic dilatation.

other demographic characteristics and traditional cardiac risk factors (Table 3).

4. Discussion

The present prospective study evaluated asymptomatic patients with T2DM for perfusion abnormalities on stress testing. Angina was ruled out by the administration of the Rose questionnaire at the time of enrollment into the study, thereby recruiting patients with no reason to suspect CAD. The patients were on contemporary medical treatment. Glycemic control was however suboptimal (mean HbA_{1c} 7.9 ± 1.5%).

Ten patients (10.3%) had evidence of silent myocardial ischemia. The prevalence of perfusion abnormalities in our study is similar to that observed in the large-scale screening study performed by the Milan Study on Atherosclerosis and Diabetes (MiSAD) group which combined treadmill exercise ECG test and SPECT.[6] This study had estimated the prevalence of unrecognized silent myocardial ischemia in patients with T2DM at 12% by exercise stress tests alone

Table 3
Comparison between patients with normal stress tests and those with abnormal myocardial perfusion.

Parameter	Stress test normal	Stress test abnormal	*P* value
N	87	10	
Demographics			
Age (years)	52.7 ± 8.4	58.4 ± 4.3	0.039
Sex			
Men (%)	65.5	80	0.489
Women	34.5	20	
Diabetes related			
Duration (years) (IQR)	5.25 (1–8)	5.4 (1–8)	0.634
HbA_{1c} (%)	7.9 ± 1.6	8.3 ± 1.3	0.388
Cardiac related			
BMI (kg/m^2)	25.7 ± 4.0	23.7 ± 2.7	0.124
Past/current smoker (%)	12.6	50	0.010
Family history of CAD (%)	6.9	10	0.545
BP > 140/90 mmHg or hypertension treatment (%)	74.7	70.0	0.714
Lipid abnormality (%)	11.5	10.0	1.000
Lipid-lowering treatment (%)	45.9	30.0	0.505

BMI: body mass index; BP: blood pressure CAD: coronary artery disease; HbA1c: glycosylated hemoglobin; IQR: interquartile range.

and at 6.4% by the combined use of exercise ECG tests and thallium scintigraphy.

However, the prevalence was lower than that reported in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (16%)[7] and the study by Lorenzo et al (26%),[8] both of which had used SPECT for evaluation of asymptomatic ischemia in diabetic patients. In the DIAD study, the largest study on this subject till date, 561 patients with T2DM, aged 50–75 years, with no known or suspected CAD, were assigned to stress testing. A total of 113 patients (22%) had silent ischemia, including 83 with regional myocardial perfusion abnormalities and 30 with normal perfusion but other abnormalities (i.e., adenosine-induced ST-segment depression, ventricular dilation, or rest ventricular dysfunction). Moderate or large perfusion defects were present in 33 patients (5.8%). The DIAD study identified abnormal Valsalva, male sex, and diabetes duration, but not traditional cardiac risk factors or inflammatory and prothrombotic markers, as predictors for abnormal tests. Similarly, in another study, one-third of diabetic patients with at least 1 additional cardiovascular risk factor had silent ischemia.[9]

Even higher rates of abnormal stress tests (40–60%) and of high-risk findings (approximately 20%) have been reported in large retrospective series in asymptomatic diabetic patients. However, referral bias may have affected the results of these studies.[10]

Small studies have been reported from India using exercise electrocardiography to estimate the prevalence of asymptomatic ischemia in T2DM. The prevalence rates were estimated at 21.1% ($n = 161$),[11] 28.9% ($n = 76$),[12] 23.6% ($n = 89$),[13] 31.4% ($n = 102$),[14] and 11% ($n = 200$)[15] in studies from Central India, Delhi, Uttar Pradesh, Rajasthan, and Maharashtra, respectively. To the best of our knowledge, no study on detection of silent ischemia in diabetic patients using SPECT has been reported from India.

The lower rates in our study likely reflect differences in the patient selection. The subjects in the present study were younger with mean age of 53.3 ± 8.3 years than those aged 60.7 ± 6.8 years in the DIAD study. However, it should be noted that in the present study, the perfusion defects were classified as small, medium, and large corresponding to involvement of <10%, 10–20%, and >20% of LV myocardium, respectively. These limits are stricter than those used in previous studies using SPECT. Overall, almost two-thirds of the abnormalities found in our study were moderate or large and involved >10% of the LV. This is in contrast to the DIAD study in which the majority of defects were small (defined as

involvement of <5% of LV myocardium) which was consistent with the notion that asymptomatic ischemia is associated with less extensive CAD. Thus, although the prevalence noted in the present study was lower than that in the previous studies, the defects were indicative of more extensive CAD.

Demographic variables and traditional cardiac risk factors were analyzed. Age and smoking were associated with increased risk for detection of perfusion abnormalities. Other traditional cardiac risk factors (hypertension, family history, or dyslipidemia) did not emerge as significantly predictive of abnormal tests.

A limitation of the present study is that a follow-up coronary angiogram was not performed in patients with moderate reversible perfusion defects. Technical artifacts such as photon attenuation, breast attenuation, and attenuation of inferior wall by extracardiac structures such as the diaphragm can lead to artifactual defects. Lack of follow-up coronary angiograms limits determination of false positive findings. However, it should be noted that soft tissue attenuation correction algorithms were applied during the acquisition of images. Second, in the institutional protocol, the exercise in myocardial perfusion imaging was symptom limited and therefore stopped even if the patient had not reached the target heart rate. In our study, 85% of age-predicted maximum heart rate was achieved in only 65 of 97 patients (67%). This could be one of the reasons for the lower rates of ischemia in the study.

5. Conclusion

The present study is the first investigation to use myocardial perfusion imaging for screening for silent ischemia in Indian patients with T2DM. About 90% of patients with no clinical evidence of CAD were found to have normal myocardial perfusion with half of the remaining patients having scar and the other half having small- to moderate-sized area ischemia. This figure is lower than the prevalence reported previously, and none of the patients had large-area ischemia. Age and smoking were associated with increased risk for detection of asymptomatic ischemic heart disease.

Conflict of interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2018.08.023.

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