Non-Invasive Assessment of Myocardial Perfusion Abnormality in Type 2 Diabetic Patients Without Symptoms of Coronary Artery Disease by SPECT-MPI

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ABSTRACT

Introduction: Coronary artery disease (CAD) is the most common chronic macrovascular complication of diabetes mellitus. Diabetic patients have a high incidence of silent ischemia and MI due to autonomic neuropathy. SPECT imaging is a well-established, non-invasive procedure that offers perfusion and functional information for diagnosis and risk stratification, facilitating the early detection of CAD. Objective: To detect myocardial perfusion abnormality by SPECT-MPI in type 2 diabetic patients without symptoms of CAD. Methods: A total of eighteen diabetic patients with no history of typical CAD, with or without risk factors, underwent gated SPECT-MPI using 99mTc-sestaMIBI. A single-day stress–rest protocol with adenosine was done in each patient. Result: Six out of eighteen patients (33.3%) showed abnormal scans suggestive of myocardial ischemia or infarction. Four of these patients had reversible perfusion defects, one had a fixed perfusion defect, and one had a mixed defect. Among these patients, single vessel territory was involved in three patients, and three patients had involvement in double vessel territories. Regarding the summed stress score (SSS) value, most of the patients (four) had mild risk, whereas moderate and severe risk of a future cardiac event were observed in one patient each. In addition, two patients had left ventricular dysfunction (EF< 45%). Five patients with normal MPI and two patients with abnormal myocardial perfusion scans had high transient ischemic dilatation (TID). Risk factors such as male sex, hypertension, hyperlipidemia, obesity, and family history of CAD were not significantly correlated with abnormal scans. But abnormal scans were significantly related to a longer duration of diabetes (P = 0.038). Conclusion: This study showed that despite being asymptomatic, a considerable portion of diabetic patients had perfusion abnormalities, not just ischemia but also infarctions. Moreover, some of these patients are at high risk for future cardiac events as assessed by SSS, TID, and LVEF.

Key words: Silent myocardial ischemia, Diabetes mellitus, Gated SPECT MPI

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INTRODUCTION

Coronary artery disease (CAD), the most common chronic macrovascular complication of diabetes mellitus, is the leading cause of morbidity and mortality in diabetic individuals (1). Around 80% of diabetic individuals die from cardiovascular disease, with coronary artery disease accounting for 75% of these deaths (2). Coronary heart disease (CHD) with type 2 diabetes may present without warning as an acute myocardial infarction (AMI), heart failure, arrhythmia, or sudden death. The existence of type 2 diabetes mellitus increases mortality in AMI and heart failure, highlighting the potential value of identifying high-risk asymptomatic individuals (3, 4). An additional feature of CAD in these patients is that they may have atypical symptoms or be asymptomatic, a condition referred to as silent or asymptomatic myocardial ischemia (4). Autonomic neuropathy influences myocardial blood flow, a well-known complication of diabetes that can produce perfusion abnormalities (5). The reported prevalence of silent ischemia in diabetic patients ranged from 6% to 59% in different studies (6–11).

Myocardial perfusion scintigraphy has been a popular technique for evaluating CAD since the inception of clinical nuclear cardiology. Various studies have specifically proven its prognostic efficacy in patients with diabetes (12). In studies comparing myocardial perfusion imaging and stress echocardiography, myocardial perfusion imaging was found to have a superior sensitivity for detecting multi-vessel and single vessel coronary artery disease (13). Moreover, perfusion abnormalities on SPECT imaging frequently denote more extensive and severe ischemia than predicted by coronary angiography (14). Quantitative gated SPECT-MPI is a powerful diagnostic modality being used for risk stratification and

the determination of prognosis in CAD. Stress myocardial perfusion imaging (MPI) may be explored for advanced cardiovascular risk assessment in asymptomatic persons with diabetes, according to the American College of Cardiology (ACC) practice guidelines (class IIb). The European Society of Cardiology has proposed a similar degree of recommendation (class IIb) for screening selected high-risk diabetic individuals for the prevalence of silent MI (15).

Given the poorer prognosis of CAD in the diabetic population, earlier detection may help reduce mortality and morbidity. So, the early, accurate diagnosis of CAD in patients with diabetes is very much needed, and reliable prognostication is mandatory. Finally, no study has been conducted in our country to date for the noninvasive assessment of myocardial perfusion abnormality by SPECT-MPI in type 2 diabetic patients with no symptoms of coronary artery disease. This study aims to detect myocardial perfusion abnormalities by SPECT-MPI in patients with diabetes mellitus (DM) who have no symptoms of CAD, with the objective of augmenting early interventional therapy, developing patient awareness about atypical signs of myocardial infarct, and complying with risk factor modification regimens.

PATIENTS AND METHODS

A cross-sectional observational study was conducted in the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), BSMMU campus, Shahbagh, Dhaka, from March 2020 to June 2021 as a fulfillment of the requirement of an MD (residency) degree in nuclear medicine under Bangabandhu Sheikh Mujib Medical University (BSMMU). Ethical approval was obtained from the Medical Research Ethics Committee (MREC) of NINMAS. Informed written consent was obtained from the study subjects with strict confidentiality of the procedure and study results. Type 2 diabetic patients referred to the nuclear cardiology division of NINMAS for screening of CAD with no current symptoms of CAD were selected for the study. Eighteen type 2 diabetes mellitus participated in the study and their age, gender, diabetes duration, and risk factors (hypertension, dyslipidemia, smoking, family history of IHD) were documented. SPECT MPI was performed to note normal MPI, reversible perfusion defect, fixed perfusion defect, transient ischemic dilatation (TID), LVEF, wall motion abnormality, summed stress score (SSS), and summed difference score (SDS).

Study procedure

An individual patient's data, including case history (age at onset of diabetes, duration of diabetes, current medication), risk factors (i.e., smoking, obesity, hypertension, dyslipidemia), and family history of IHD for the patient, were recorded. Predetermined data collection sheets, supplemented by documentary evidence, were used. After a thorough medical history and clinical examination of the patient, ECG, echocardiography, and gated SPECT (GSPECT) MPI were done. For GSPECT-MPI, a one-day stress-rest protocol was followed, and pharmacological stress was done by injection of adenosine at a dose of 140 g/kg body weight per minute for 6 minutes. The radiopharmaceutical ^{99m}Tc-sestamibi was injected both at stress (7–10 mCi) and rest (15–25 mCi). SPECT image acquisition was done approximately 30–90 minutes after radiopharmaceutical injection, both under stress and at rest. After getting the GSPECT MPI report, enrolled subjects were divided into two groups: Normal myocardial perfusion: normal SPECT MPI (Group I); and presence of a myocardial perfusion defect: abnormal SPECT MPI (Group II). Analysis was done to see the effect of independent variables (age, sex, duration of diabetes, and risk factors) on dependent variables (normal and abnormal MPI reports).

Statistical analysis

Collected data was analyzed by using computer based programmed Statistical Package for Social Sciences (SPSS) software (Version - 26) for Windows (SPSS Inc., Chicago, Illinois, USA). Qualitative variables were expressed as frequencies, percentages. Quantitative variables were expressed as mean ± standard deviation. Result of significance has been expressed as p-value and statistical analysis was performed by Chi-square/unpaired t-test and a value $p<0.05$ was considered as statistically significant.

RESULTS

A total of 18 diabetic patients (M = 15, F = 3), aged between 42 and 73 (59.38±10.22) years, had a history of type 2 DM for a period of 4 to 15 (8.22±2.88) years). Four patients had diabetes for less than five years, while 14 had it for more than five years. About 77.8% (14 patients) were on treatment with an oral hypoglycemic agent (OHA), and the rest of the 22.2% (4 patients) were on insulin (Table 1). Table 1 depicts the distribution of the study population based on risk factors. A significant number of patients (55.5%) were former smokers, with 66.7% hypertensive, 55.6% dyslipidemic, and 55.6% having a family history of IHD. Fourteen patients (77.8%) had a normal BMI, and four (22.2%) were overweight.

Table 1: Distribution of the study population by risk factors (n=18).

Risk factors	n	%
Smoking		
Non smoker	05	27.8
Past smoker	10	55.5
Smoker	03	16.7
BMI		
Normal (18.5-24.9)	14	77.8
Overweight (25.0-29.9)	04	22.2
HTN		
Yes	12	66.7
No	06	33.3
Dyslipidemia		
Yes	10	55.6
No	08	44.4
Family history of IHD		
Yes	10	55.6
No	08	44.4

Among the 18 patients who underwent gated MPI, 12 had normal myocardial perfusion (Group I), and six showed abnormal myocardial perfusion, suggesting ischemia or infarction (Group II).

Out of six patients with abnormal MPI findings, four had a reversible perfusion defect, one had a fixed defect, and one patient had both a reversible and a fixed defect. One patient had less than 10% myocardial involvement, four patients had more than 10%–20%, and one patient had more than 20% myocardial involvement. Three of these patients had single vessel territory involvement (two in the RCA and one in the LCX), while the other three had double vessel territory involvement (LAD and LCX).

Among the six patients in Group I risk stratification was done by SSS, SDS and LVEF. It was observed that four patients had mild risk (SSS 4-8) followed by one moderate risk (SSS 9-13) and one severe risk (SSS > 13) of a future cardiac event. Two patients had mild (SDS 2-4), one patient had moderate ischemia (SDS 5-8) and two patients had severe ischemia (SDS >8). One patient had fixed defect or MI (SDS 0). In this group, four patients had normal LVEF (>45%) and two patients had low LVEF (<45%).

A comparison of the patients by demographic characteristics like age and gender is shown in Table 2. It was observed that there was no statistically significant (p>0.05) difference in terms of demographic characteristics between the two groups.

Table 2: Comparison of the study population according to demographic characteristics and GSPECT-MPI findings (n=18).

Demographic characteristics	Group I (n=12)		Group II (n=6)		p value
	n	%	n	%	
Age (in years)					
<50	2	16.7	3	50.0	
50-60	3	25.0	2	33.3	
61-70	4	33.3	0	0.0	
>70	3	25.0	1	16.7	
Mean ± SD	61.58±10.43		55.0±9.03		[a]0.207[ns]
Range (Min, Max)	(42,73)		(48,71)		
Sex					
Male	9	75.0	6	100.0	[b]0.179[ns]
Female	3	25.0	0	0.0	

ns= not significant

[a]p value reached from unpaired t-test

[b]p value reached from Chi-square test

Table 3 shows the comparison between risk factors and patients with normal (Group I) and abnormal (Group II) myocardial perfusion. There was no statistically significant (p > 0.05) difference between the two groups in terms of smoking, BMI, HTN, dyslipidemia, and family history of IHD.

Table 4 shows the comparison between MPI findings and diabetes status. The mean duration of diabetes was 7.25±2.09 years in group I and 10.17±3.43 years in group II.

Table 3: Comparison of the study population according to SPECT-MPI and risk factors (n=18)

Risk factors	Group I (n=12)		Group II (n=6)		p value
	n	%	n	%	
Smoking					
Non smoker	5	41.7	0	0.0	0.122[ns]
Past smoker	6	50.0	4	66.7	
Smoker	1	8.3	2	33.3	
BMI					
Normal (18.5-24.9)	9	75.0	5	83.3	0.688[ns]
Overweight (25-29.9)	3	25.0	1	16.7	
HTN					
Yes	8	66.7	4	66.7	1.000[ns]
No	4	33.3	2	33.3	
Dyslipidemia					
Yes		50.0	4	66.7	0.598[ns]
No	6	50.0	2	33.3	
Family history of IHD					
Yes	7	58.3	3	50.0	0.737[ns]
No	5	41.7	3	50.0	

ns= not significant
p value reached from Chi-square test

The difference was statistically significant (P=0.038). More than eighty percent (83.3%) of patients were on treatment with OHA in group I and 04 (66.7%) in group II. The difference was not statistically significant.

Table 4: Comparison of the study population according to SPECT-MPI findings & diabetes status (n=18).

Duration of DM (years)	Group I (n=12)		Group II (n=6)		p value
Mean±SD	7.25±2.09		10.17±3.43		[a]0.038[s]
Range (Min,Max)	(4,11)		(5,15)		
Diabetes Treatment	**n**	**%**	**n**	**%**	
OHA	10	83.3	4	66.7	[b]0.422[ns]
Insulin	2	16.7	2	33.3	

s= significant
ns= not significant
[a]p value reached from unpaired t-test
[b]p value reached from Chi-square test

Table 5 shows comparison of study population by TID in SPECT-MPI findings. It was observed that total 07 (38.8%) out of 18 patients had high TID. More than half (58.3%) of the patients had normal TID in group I and 04 (66.7%) in group II. High TID (>1.1) was seen in 41.7% of patients of group I and 33.3% of patients of group II. The difference was not statistically significant (p>0.05) between the two groups.

Table 5: Comparison of the study population by TID (n=18).

TID	Group I (n=12)		Group II (n=6)		p value
	n	%	n	%	
Normal	7	58.3	4	66.7	0.732[ns]
High	5	41.7	2	33.3	

ns= not significant
p value reached from Chi-square test

Table 6 shows comparison between the two groups according to wall motion abnormality seen in GSPECT-MPI test. It was observed that total 04 (22.2%) patients out of 18 patients had abnormal wall motion. Ten (83.3%) patients had normal wall motion in group I and 04 (66.7%) in group II. Two patients had wall motion abnormality both in group I and II. The difference was not statistically significant (p>0.05) between the two groups.

Table 6: Comparison of the study population by wall motion abnormality (n=18).

Wall motion abnormality	Group I (n=12)		Group II (n=6)		p value
	n	%	n	%	
Normal	10	83.3	4	66.7	0.422[ns]
Abnormal	2	16.7	2	33.3	

ns= not significant
p value reached from Chi-square test

Table 7 shows the distribution of the study population by ECG. Hundred percent (100.0%) patients had normal ECG in group I and 05 (83.3%) in group II. The difference was not statistically significant (p>0.05) between the two groups.

Table 7: Comparison of the patients by baseline ECG (n=18).

ECG	Group I (n=12)		Group II (n=6)		p value
	n	%	n	%	
Normal	12	100.0	5	83.3	0.145[ns]
Abnormal	0	0.0	1	16.7	

ns= not significant
p value reached from Chi-square test

Table 8 shows comparison of the patients by echocardiography. More than ninety percent (91.7%) of patients had normal echocardiography in group I and 83.3% in group II. Only two patients had abnormal wall motion in echocardiography, one in each group. The difference was not statistically significant (p>0.05) between the two groups.

Table 8: Comparison of the patients by echocardiography (n=18).

Echo	Group I (n=12)		Group II (n=6)		p value
	n	%	n	%	
Normal	11	91.7	5	83.3	0.595[ns]
Abnormal	1	8.3	1	16.7	

ns= not significant
p value reached from Chi-square test

DISCUSSION

Noninvasive testing has been utilized in an attempt to identify asymptomatic diabetic patients with silent coronary artery disease. There are various diagnostic tests to diagnose CAD, but they all have their own limitations. The large volume of evidence supporting the prognostic value of gated SPECT MPI renders it particularly appealing for screening asymptomatic DM patients (16). The diagnostic accuracy of exercise, dipyridamole, adenosine, and dobutamine myocardial perfusion imaging in detecting >50% coronary stenosis defined angiographically ranges from 69% to 96%, 77% to 97%, 80% to 95%, and 66% to 94%, respectively (17).

In this study, six diabetic patients (33.3%) had evidence of asymptomatic myocardial perfusion abnormalities. Most of the perfusion abnormalities were reversible defects that could pose an increased risk for future adverse cardiovascular events. The prevalence of abnormal myocardial perfusion in asymptomatic diabetes was within the reported range of 17% to 59% (6–11, 18, 19).

The perfusion abnormalities detected in this study are quite similar to those detected in the studies performed by Salehi et al., (2015) (37.7%) (12), Al Humaidet al., (2007) (37%) (20), and Valensi et al., (2005) (30.7%) (19). Our study's prevalence of myocardial perfusion defects is similar to that reported in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (22%), as well as the study by De Lorenzo et al. (2002) (26%), both of which used SPECT to evaluate asymptomatic ischemia in diabetic patients. In the DIAD study, the largest study on this topic to date, 1123 patients with type 2 diabetes mellitus (T2DM), aged 50–75 years, with no known or suspected CAD, were assigned to stress testing. A total of 22% of patients 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 (8).

In retrospective database analyses of patients with diabetes referred for stress testing, a high prevalence (41–58%) of abnormal stress myocardial perfusion imaging and a high cardiac event rate were found (10, 22, 23) probably due to the inclusion of both symptomatic and asymptomatic diabetic patients.

Despite the fact that diabetes raises the relative cardiovascular risk in women more than in men, males still have a higher absolute risk of cardiovascular events than women (24). Although a larger percentage of men in our population had silent ischemia compared to women (none among the three), the difference was not significant. However, male sex was a strong predictor of abnormal scans in studies with a larger number of participants (1, 8, 10, 21).

The findings that age was not associated with the occurrence of silent ischemia in this study are supported by earlier studies (1, 8). However, in two other separate studies, silent ischemia was found in older patients (10, 19). According to Chaowalit et al. (2006), the prevalence of inducible ischemia is significantly higher in patients with type 2 diabetes over the age of 65 (25). In this current study, no association of age with silent ischemia was found, probably due to the small sample size.

Multiple cardiac risk factors are common in patients with T2DM, including hypertension, dyslipidemia, inactivity, smoking, and obesity. Multiple risk factors in the same patient substantially increase the overall cardiovascular risk (26). Conventional risk factors such as smoking, hypertension, hyperlipidemia, and obesity were not predictive of silent ischemia in our study, supporting earlier findings (8, 12).

The observation in this study that patients with a history of diabetes >10 years were linked to more abnormal scans is supported by prior research performed by Anand et al. (2006) (27) and Wackers et al. (2004) (8). DIAD study found strong association between moderate or large perfusion abnormalities with symptoms of autonomic neuropathy, but such association was not evaluated in this study.

It should be noted that in the present study, the perfusion defects were classified as small, medium, and large, corresponding to the involvement of <10%, 10–20%, and > 20% of the LV myocardium, respectively. Overall,

almost 2/3 of the abnormalities found in this study were moderate, which is similar to the study performed by Deepti et al. (2018) (4). This is in contrast to the DIAD study (8) in which the majority of defects were small (defined as involvement of <5% of the LV myocardium), which was consistent with the notion that asymptomatic ischemia is associated with less extensive CAD.

The study subjects were categorized by transient ischemic dilatation in SPECT-MPI evaluation, with 38.8% having high TID, which might be attributed to the presence of subendocardial or balanced ischemia. In another study, it was shown that TID in diabetic patients without regional myocardial perfusion abnormalities is an important sign of CAD, especially when the TID ratio exceeds 1.16 (12). This means that patients with asymptomatic diabetes have not only higher abnormal perfusion but also ventricular functional compromise.

Wall motion abnormalities and low LVEF (45%) were two significant findings of this study, which was observed in patients of both normal and abnormal SPECT-MPI but other research did not assess these points.

CONCLUSION

This study showed that a significant portion of patients had myocardial perfusion defects that not only caused ischemia but also infarctions, though they were asymptomatic. It is expected that asymptomatic patients should have small perfusion defects, but the current study showed that most of the patients had moderate-sized perfusion defects. This study also showed that perfusion abnormalities are significantly related to the long duration of diabetes. Moreover, some of these patients are at high risk for future cardiac events as assessed by SSS, TID, and LVEF. This study indicates that gated SPECT-MPI can facilitate the early detection of the frequency and extent of myocardial perfusion abnormalities in asymptomatic patients with long-term diabetes who are at risk for future adverse cardiac events. Assessment of diabetic patients for silent ischemia by SPECT-MPI may result in early initiation and more aggressive risk factor intervention. Further studies with larger patient groups are necessary to compare the prevalence of silent ischemia in diabetic patients with that in the normal population.

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