

Assessing the Prevalence and Predicting Factors of an Abnormal Gated Myocardial Perfusion SPECT in Asymptomatic Patients with Type 2 Diabetes

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Abstract

Abstract Introduction: Considering the significant prevalence of silent myocardial ischemia and its related morbidity and mortality in asymptomatic type two diabetic patients, it is not well known whether early screening with MPI is cost-effective. However, predicting factors are not elucidated. **Materials and Methods:** This was a cross-sectional study including 63 asymptomatic patients with type 2 diabetes mellitus (T2DM), with normal ECG and ejection fraction. Patients with any history of documented valvular, congestive or ischemic heart disease, renal or hepatic failure were excluded. At first all patients were interviewed and checked for risk factors and then patients underwent a two-day rest/stress 99mTc-MIBI gated MPI SPECT. Data was assessed by QPS/QGS and 4DM software and evaluated by a nuclear medicine specialist with summed stress score (SSS) of more than 4 defined as CAD. **Results:** There were 42 females (67%) and 21 males (33%), with a mean age of 61.33 ± 6.98 years and 7.97 ± 4.86 years history of T2DM. CAD was detected in 26 (41.3%) patients and was significantly associated with male gender, smoking, requiring insulin therapy and EF (P-value = 0.019, 0.046, 0.05, 0.033, respectively). A significant association was found between the duration of diabetes, especially when $>15y$, and the probability of having CAD. Multivariable logistic regression revealed that smoking; male gender and diabetes duration were the strongest independent predictors of abnormal MPI results. **Conclusion:** We found a high (46%) prevalence of abnormal stress MPI SPECT in patients with type 2 diabetes mellitus, despite being asymptomatic. Asymptomatic patients with a history of smoking, long duration of diabetes, being under insulin treatment and male gender might benefit from MPI for early detection of silent ischemia. **Keyword:** 99mTc-MIBI; Gated Myocardial Perfusion Imaging; Type 2 Diabetes Mellitus; Silent Ischemia; Asymptomatic CAD; Early Screening

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Highlights:

- The prevalence of type2 DM is increasing
- Many patients with type 2 diabetes develop CAD
- The optimal CAD screening tool for diabetics is unknown
- Myocardial perfusion study (MPS) is a non-invasive and effective diagnostic method for CAD
- Which asymptomatic diabetics would benefit the most from MPS is controversial.
- Type 2 diabetics with longer duration of diabetes, smokers and insulin users are at greater risk of asymptomatic CAD

Introduction

The global prevalence of type 2 diabetes mellitus (T2 DM), an essential risk factor for coronary artery disease (CAD), is on the rise (1, 2). On the other hand, CAD as a major cause of morbidity, mortality, and financial costs in patients with T2DM, could be asymptomatic in 20–35% of diabetic patients (3). However, acute myocardial infarction (MI) and sudden cardiac death might be often the initial presentations (4, 5). Developing at a younger age, higher rate of multi-vessel disease and being more prone to have complications after MI, such as congestive heart failure, are some of the features indicating the overall poorer outcome of CAD in diabetic patients (6-8). This further emphasizes the importance of detecting CAD at an early stage in these patients (9). It has been suggested that myocardial perfusion imaging (MPI) is a reliable technique for risk assessment of CAD in diabetic patients (10-12). It is still under debate whether screening myocardial ischemia is rational in asymptomatic diabetic patients compared to standard therapeutic strategies and whether it improves the risk stratification, management, and prognosis in different patient groups (4). Therefore, the aim of this study was to assess CAD risk, prevalence and Predicting Factors of an Abnormal Gated Myocardial Perfusion SPECT in Asymptomatic Patients with Type 2 Diabetes .

Materials and Methods

This was a cross-sectional study, conducted at the nuclear medicine department of Shohada Tajrish hospital, Tehran, Iran. In total, 63 asymptomatic patients with type 2 DM, referred for check-up or pre-operative cardiac evaluation entered the study. An ethical approval was obtained from Shahid Beheshti Medical University Ethics committee.

Patients were interviewed on the appointed scanning day and informed about the goals of study in detail. A written informed consent was obtained from all patients before enrolment. The inclusion criteria were patients with proven T2DM, aged 35-80 years, ejection fraction (EF) > 50%, normal ECG and life expectancy of more than one year. Patients with any history of valvular heart disease, ischemic heart disease, abnormal renal or hepatic failure, coronary intervention, arrhythmia, perfusion defect on prior MPI scans or wall motion abnormality on prior gated stress SPECT-MPI were excluded. Demographic characteristics of participants were documented in a questionnaire. All patients underwent a two-day rest/stress 99mTc-MIBI gated MPI SPECT, according to the European Association of Nuclear Medicine (EANM) guidelines for MPI scan

(13). The rest scan was performed 60 minutes after IV injection of 555 MBq 99mTc-sestamibi. On the day after, myocardial stress was achieved by exercise (Bruce protocol) or Dipyridamole (0.14mg/kg/min over 4 minutes), with 740 MBq 99mTc-sestamibi injected at peak stress. All patients consumed 120 mL whole milk 10 minutes after tracer injection, as per routine. Imaging was performed in both supine and prone positions. SPECT images were acquired with a variable angle dual head Evo-Voxel Siemens gamma camera (64 projections; 25 seconds/projection, matrix 64 * 64, zoom of 1.46, 8-frame gated study, low-energy high resolution collimator, in a noncircular orbit). The images were processed using QPS/QGS and 4DM software and the results were interpreted by a nuclear medicine specialist.

Statistical Analysis

Descriptive data were reported as mean and standard deviation for quantitative variables and number and percentage for qualitative variables. T-test was used to compare the means between the two groups. For all tests, a P-value below 0.05 was considered statistically significant. SPSS version 20 (SPSS Inc., Chicago, IL, The USA) was used for data analysis.

Results

Of 63 patients, 42 were females (67%) and 21 males (33%), with a mean age of 61.33 ± 6.98 years (range: 42-78). The mean \pm SD duration of diabetes was 7.97 ± 4.86 years. Baseline characteristics of participants are presented in Tables 1 & 2.54 patients underwent stress with Dipyridamole, 2 with Dobutamine and 7 with exercise.

According to the obtained values of MPI (true SSS > 4, without attenuation artifacts), CAD was detected in 26 (41.3%) patients. Presence of CAD was significantly associated with male gender, smoking and EF (P-values; 0.019, 0.046, 0.033, respectively). While hypertension and dyslipidemia were more common in CAD patients compared to those without CAD, no statistically significant association was noted (P-value > 0.05) (Table 3).

Moreover, patients were divided into five groups based on the duration of diabetes. Kruskal Wallis analysis revealed a significant correlation between the duration of diabetes, especially when more than 15 years, and the probability of CAD, based on SSS, SDS especially in LAD territory (P-value = 0.048) (Figures 1). Besides, requiring Insulin therapy was significantly more prevalent in diabetic patients with CAD compared to those without CAD (P-value = 0.042). (Figure 2)

Mean EDV and ESV were higher in CAD patients compared to diabetic patients without CAD (68.52 ± 3.41 and 29.35 ± 2.14 mL versus 52.72 ± 2.23 and 18.52 ± 1.47 mL). However, the difference was not statistically significant (P-value > 0.05).

According to multivariate logistic analysis, smoking had a significant association with SDS, RCA territory involvement and RV visualization. In addition, duration of DM was significantly associated with higher SSS and SRS, presence of TID, and RCA/LAD territory involvement. Smoking, male gender and diabetes duration were the strongest independent predictors of abnormal MPI results.

Univariate linear regression analysis showed an association between SSS, SRS, LAD/RCA territories involvement and TID with the duration of diabetes. SRS, RCA territory involvement and EF were also independently associated with hyperlipidemia. LAD territory involvement was associated with insulin therapy, HTN, and RV visualization. TID was associated with neuropathy and peripheral arterial disease (PAD). SDS was associated with B-blocker therapy.

Table 1. Demographic characteristics of the study participants

Male/female	21(33.33%)/42(66.67%)
Age(years)	61
Diabetes duration(years)	7.97
Treatment	Treatment

Male/female	21(33.33%)/42(66.67%)
Insulin	14 (22.22%)
Insulin+oral agent	10 (15.87%)
Oral agent	39 (61.90%)
Retinopathy(yes/no)	10 (16.13%)/52(83.87%)
Peripheral vascular disease	6 (9.68%)/56(90.32%)
ASA	24 (42.11%)
HTN (yes/no)	35 (55.56%)/28(44.44%)
HLP (yes/no)	36 (57.14%)/27(42.86%)
Mean TG	121
Mean Cholesterol	169
Mean HDL mg/dl	41
Mean LDL mg/dl	94
Mean BMI	28.60
HbA1c%	7.1
Smoking (yes/no)	10 (5.87%)/53(84.13%)
Neuropathy (yes/no)	5 (8.20%)/56(91.8%)
Nephropathy (yes/no)	7 (11.48%)/54(88.52%)
Family history (yes/no)	9 (14.52%)/53(85.48%)
b-blocker	25 (40.98%)
Statin	39 (63.93%)
ACE inhibitor	33 (56.90%)

*Based on Chi-Square Test; HTN= hypertension; HLP= high lipid profit; DIP= dipyridamole. TG: Triglyceride,

HDL: High density lipoprotein, LDL: Low density lipoprotein, BMI: Body mass index, ACE : Angiotensin-converting enzyme

Table 2. MPI SCAN Results

Index	Mean \pm SD
EDV	59.54 \pm 2.87
ESV	22.44 \pm 1.65
EF	56.93 \pm 8.84
SDS	2.51 \pm 3.53
SRS	1.38 \pm 2.84
SSS	4.00 \pm 4.35
Dilated LV	5(7.94%)
RV	4(6.35%)
TID	6(9.52%)
LCX	8(12.70%)
LAD	23(36.51%)
RCA	11(17.46%)

EDV: End diastolic value, ESV: End systolic value, EF: Ejection fraction,

SDS: Summed difference score, SRS: Summed rest score, SSS: Summed stress score,

LV: left ventricle, RV: Right ventricle, TID: Transient ischemic dilatation,
 LCX: Left circumflex artery, LAD: Left ascending artery, RCA: Right coronary artery

Table 3. Comparing Patients with Normal and abnormal MPI Scan

Variable	Non-CAD	CAD	P value
N	37(58.7%)	26(41.3%)	
Age	59.35±6.26	64.15±7.09	0.301
Male/female	8(21.6%)/29(78.4%)	13(50%)/13(50%)	0.019
HbA1c	7.73±2.16	7.11±1.23	0.155
HTN	18(48.6%)	17(65.4%)	0.118
HLP	20(54.1%)	16(61.5%)	0.371
SMOKING	4(26.9%)	7(10.8%)	0.094
Neuropathy	2(5.6%)	3(12%)	0.329
Retinopathy	6(16.7%)	4(15.4%)	.584
Nephropathy	6(16.7%)	1(4%)	0.131
PAD	2(5.6%)	4(15.4%)	0.196
FH	6(16.7%)	3(11.5%)	.427
B-blocker	11(31.4%)	17(53.8%)	.078
ASA	13(46%)	11(44%)	.798
ACEI	17(53.1%)	16(63.5%)	.354
Statins	21(60.0%)	18(69.2%)	.320
BMI	28.08±5.99	28.3±4.13	.698
EF	67.91± 9.29	63.11± 8.54	.033
EDV	52.72±3.41	68.52±2.14	.097
ESV	18.53±2.23	29.35± 1.47	.089
LV dilated	0	5(19.2%)	
RV	0	4(15.4%)	
TID	0	6(23.1%)	

HTN; Hypertension, HLP; Hyperlipidemia, PAD; Peripheral artery disease, FH; Family History, ASA; Aspirin, ACEI; Angiotensin-converting enzyme inhibitors, BMI; Body Mass Index, EF; Ejection fraction, EDV; End-diastolic volume, ESV; End-systolic volume, RV; Right ventricle, TID; Transient ischemic dilatation.

Figure 1. Duration of Diabetes in Patients With and Without CAD. Numbers in the vertical axis indicate number of patients. Color bars correspond to the duration of diabetes in year. CAD; coronary artery disease.

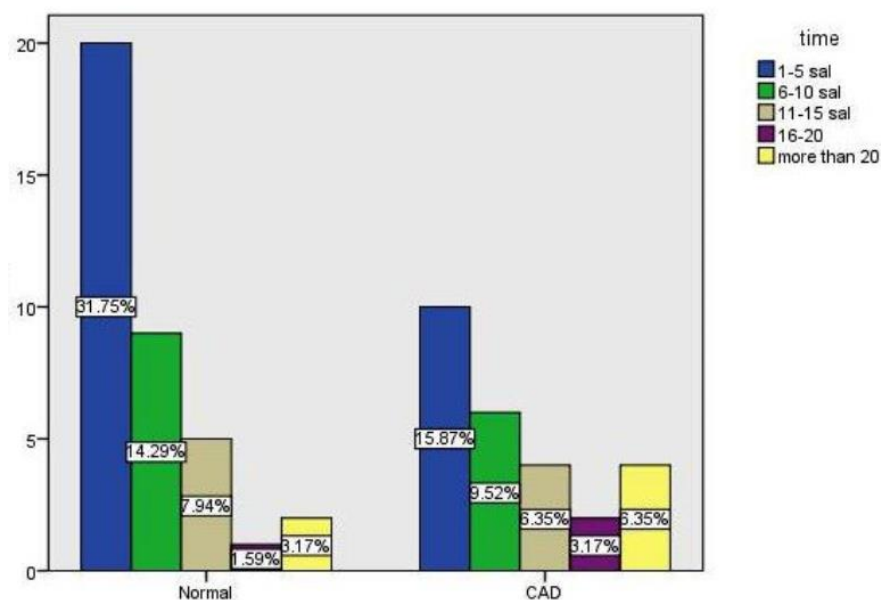
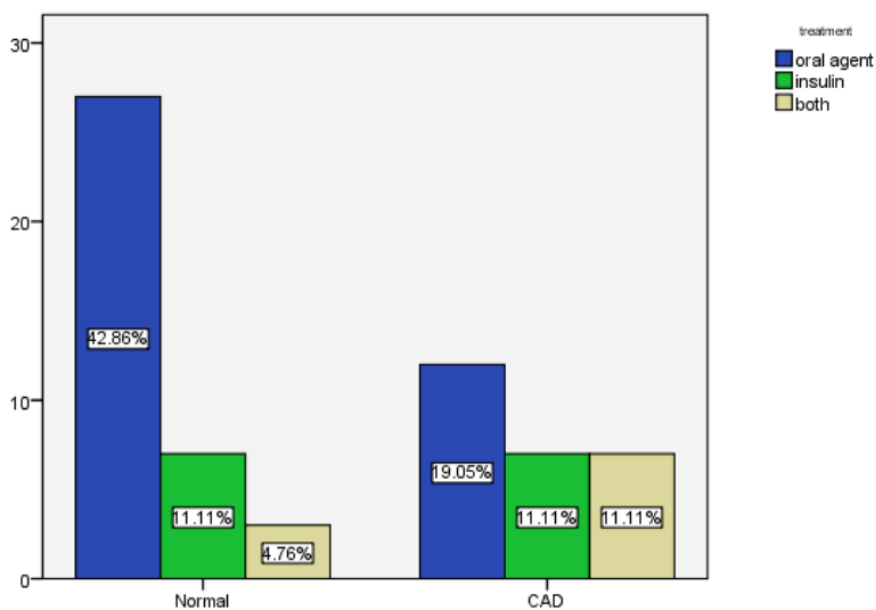


Figure 2. Type of Treatment in Patients With and Without CAD. Numbers in the vertical axis indicate number of patients.



Discussion

Many studies have been conducted to evaluate the prevalence of silent myocardial ischemia in asymptomatic diabetic patients, reporting a prevalence of 9% to 57% (14). Silent ischemia is characterized by confirmed myocardial ischemia objectively without symptoms of angina or angina equivalents(15). The autonomic neuropathy in diabetes has been proposed to be the reason for blunted perception of chest pains, justifying a

higher proportion of silent ischemia in these patients (16). The incidence of cardiovascular events and death are significantly higher in type 2 diabetic patients with MPI SPECT abnormalities (17).

Various diagnostic tests are implemented to diagnose CAD, each having their own limitations. For example, rest ECG could yield normal findings in more than a half of patients with chronic stable angina (18). Also, no agreement has been achieved on which asymptomatic diabetic patients should be screened (19, 20). Scholte et al. reported a 13% rate of cardiac deaths and cardiovascular events in patients with type 2 diabetes during a 3-year follow-up. None of the known cardiovascular risk factors have been shown to have enough sensitivity and specificity to predict silent myocardial ischemia in diabetic patients (21).

However, our study revealed a 41.3% prevalence of silent ischemia in asymptomatic type 2 diabetic patients, higher than 37% reported by Al-Humaidi et al (22). They reported that perfusion defects were related to disease duration, insulin use, nephropathy, and neuropathy. Their results regarding the duration of diabetes or insulin use was in accordance with our findings which should be examined in further studies as well.

CAD was diagnosed in our patients despite having no compromise in LVEF in echocardiography or electrocardiographic (ECG), highlighting the superior sensitivity of MPI SPECT in detecting silent ischemia/CAD. This is in accordance with the findings of Mohagheghie et al. who reported that CAD was detected by MPI in one third of asymptomatic diabetic patients with normal ECG and no evidence of peripheral arterial disease (23). Moreover, CAD was significantly more prevalent in patients with diabetes mellitus of more than 15 years, consistent with other studies which indicate an increased risk of cardiac events in prolonged diabetes mellitus (24-26).

Wu et al. reported that asymptomatic postmenopausal women with DM had a higher SSS and SDS than age-matched men (27). While our study found that male gender, regardless of smoking and requiring insulin treatment, is a strong predictor of myocardial perfusion abnormalities in asymptomatic diabetic patients. This might be due to poor control of blood sugar in men and intentional non-adherence to medications compared to women. However, women in our study were mainly pre-menopausal.

Moreover, Salehi et al, concluded that DM was independently associated with abnormal MPI in asymptomatic patients with a normal LVEF, also claiming that smoking and longer duration of DM were correlated with myocardial perfusion abnormalities, which is consistent with our findings. However, they found no significant difference between males and females in terms of abnormal MPI findings (28). This might be due to different study population or inclusion criteria.

MPI SPECT is a readily accessible, easily performed modality compared to other evolving modalities such as CT-angiography, MRI or newly discovered biomarkers, as evidence is scarce in supporting their incremental values in predicting further cardiac events. Moreover, MPI SPECT offers an automated evaluation and is less operator-dependent (29).

Our study had some limitations. Our sample size was quite small. Besides, the effect of some of possible confounding factors such as underlying liver or kidney disease (abnormal liver function tests or serum creatinine levels) was not assessed in our study, as we excluded such patients from our study. Further, prospective studies, with larger population and longer follow-ups are necessary to determine the prognostic value of an abnormal MPI in asymptomatic diabetic patients.

Conclusion

The current study revealed a high (46%) prevalence of abnormal stress MPI SPECT in patients with type 2 diabetes mellitus, despite having a normal ECG and EF in echocardiography, which in turn indicates a higher risk of fatal cardiac events, if not detected early. Smoking, duration of diabetes, requiring insulin treatment and male gender were independent predictors of abnormal MPI, proceeding to silent ischemia. These findings may assist cardiologists in choosing asymptomatic diabetic patients for early screening of CAD, thereby lowering the risk of CAD-related morbidity and mortality.

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Authors' contribution

All the authors participated in preparing the manuscript according to the ICMJE authorship criteria.

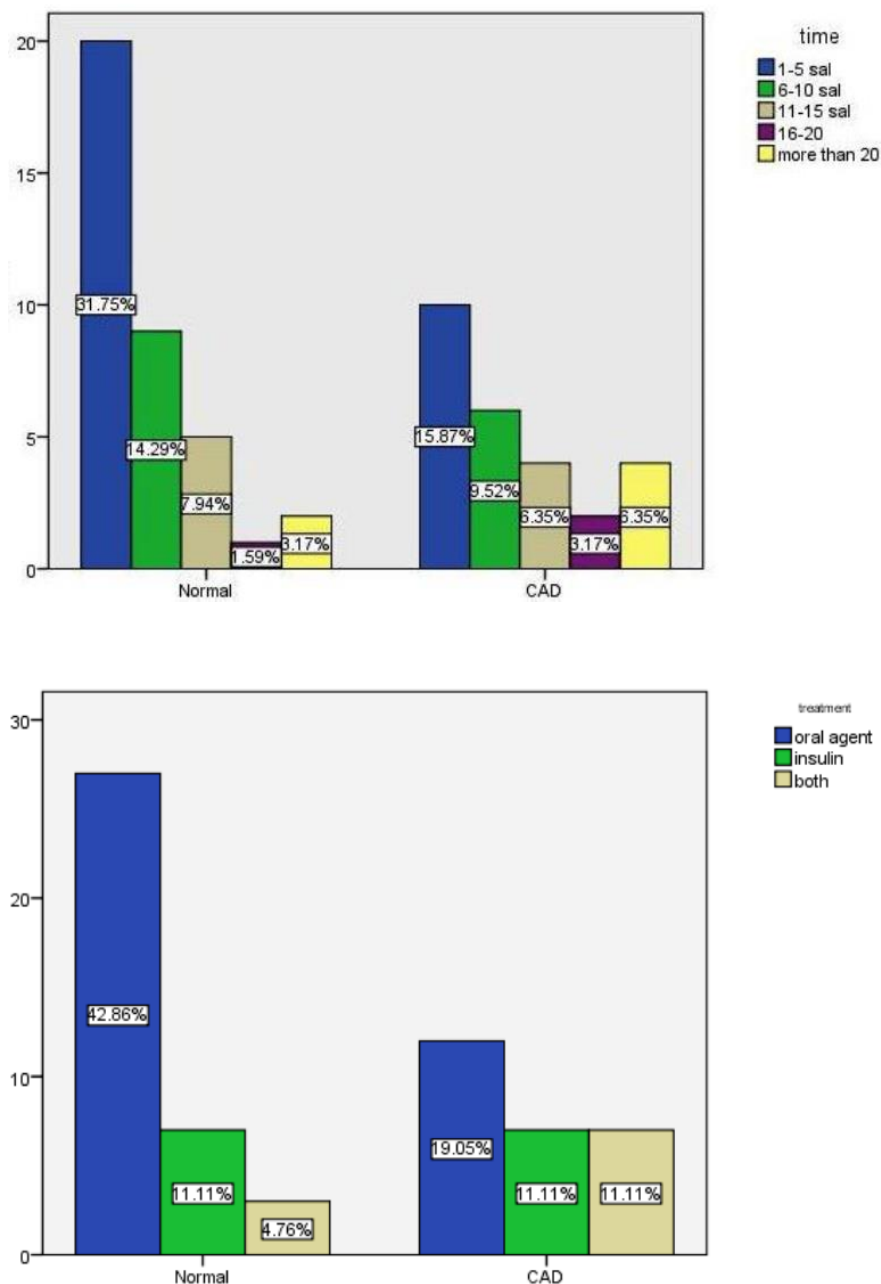
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