The Diagnostic Value of Tc-99m MIBI Gated Myocardial Perfusion SPECT in Detection of Silent Myocardial Ischemia in Asymptomatic Patients with Type 2 Diabetes Mellitus

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Abstract

Objective: In this study, we aimed to evaluate the diagnostic value of Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) gated myocardial perfusion SPECT (MPS) in the detection of coronary artery disease (CAD) and silent myocardial ischemia (SMI) in patients with asymptomatic type 2 diabetes mellitus (DM).

Materials and Methods: For this purpose, 35 patients with type 2 DM and 15 volunteers with no cardiac symptoms (control group) were included in this study. Exercise tolerance tests (ETT), echocardiography and Tc-99m MIBI gated MPS were performed in patients and volunteers. Computed tomography coronary angiography (CTCA) was performed in patients with coronary ischemia or infarct detected by Tc-99m MIBI gated MPS. The results were analyzed and compared visually and statistically.

Results: The present study revealed a high rate of silent myocardial ischemia (25.71%, N=9) in 35 patients with type 2 DM. Severe CAD in CTCA was detected in four of nine patients with ischemia or infarct by Tc-99m MIBI gated MPS (44.4%). Left ventricular diastolic dysfunction, ischemic pattern and high risk of CAD were detected in the same four patients by echocardiography, ETT and biochemical analysis, respectively. At the end of the statistical evaluation, we found that Tc-99m MIBI gated MPS showed significant correlations with CTCA, echocardiography, ETT, Hba1c level, risk of CAD and diabetic age in diabetic patients with CAD.

Conclusion: We propose that Tc-99m MIBI gated MPS is a reliable and non-invasive method that can be used to detect silent myocardial ischemia and CAD in patients with type 2 DM.

Keywords: Diabetes Mellitus, Gated SPECT, Myocardial Ischemia, Tc-99m MIBI, Gated SPECT, Type 2
Introduction

Eighty-five percent of all diabetic patients have type 2 diabetes mellitus (DM). The incidence of cardiovascular disease in diabetics is three times higher than in nondiabetics. Coronary artery disease (CAD) in patients with DM is the main reason for morbidity and mortality [1,2].

The incidence of silent myocardial infarction is more frequent in diabetics compared to the normal population, and recent studies indicate a correlation between silent myocardial ischemia (SMI) and a high mortality risk [3].

Because of its high mortality risk, it is very important to detect CAD in patients with DM early, especially with noninvasive methods [4, 5]. CAD exists in more than half of diabetics [6,7]. Although it is an important cause of mortality, CAD is often asymptomatic in patients with type 2 DM and may appear as arrhythmia, congestive heart failure, acute myocardial infarction (MI) and sudden death [8].

A variety of tests are used to indicate SMI [9, 10], including electrocardiography (ECG), exercise treadmill tests (ETT), 24-hour Holter monitoring, stress echocardiography, myocardial perfusion SPECT (MPS), coronary angiography (CA) and computed tomography coronary angiography (CTCA). The aim of this study is to evaluate the value of exercise Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) gated MPS in the detection of CAD and SMI in asymptomatic patients with type 2 DM.

Materials and Methods

Patients

In total, 50 people were included in this study; they were divided into two groups. Group A consisted of 35 patients (16 males and 19 females, 35-70 years old) with type 2 DM having at least one year of follow-up (1-22 years) with no cardiac symptoms. Group B, a control group, consisted of 15 volunteers (10 males and 5 females, 35-72 years old) with no known diseases or symptoms.

In addition to anamnesis (duration of DM, hypertension, smoking, familial CAD story, etc.), biochemical test results (plasma Hba1c, total cholesterol, HDL, LDL and triglyceride levels) were obtained before imaging for cardiac risk assessment. All patients were instructed not to consume beta-blockers or Ca channel blockers for two days and nitrates for one day before the study. All patients were warned not to eat anything 3-4 hours before the study.

A 1-day protocol of Tc-99m MIBI gated MPS rest and stress study was performed in all patients. In the stress study, the Bruce protocol was used and Tc-99m MIBI was injected after at least 85% of the age-predicted maximum heart rate was reached. ETT was ended 1 minute after Tc-99m MIBI injection, and ECG findings were followed for 10 more minutes. In total, 10 and 25 MCI Tc-99m MIBI were injected in the rest and stress studies, respectively.

Gated MPS images were acquired 45 minutes after Tc-99m MIBI injection using a large field of view dual-headed gamma camera (Siemens, Ecam) equipped with a low-energy high resolution, parallel-hole collimator. Data were obtained from 64 projections of 25 seconds each in the 140 keV photopeak over an 180° arc in a 64x64 matrix. Acquisition was synchronized with an ECG trigger, and eight frames per cardiac cycle were obtained. A short axis (SA), vertical long axis (VLA) and horizontal long axis (HLA) were reconstructed from the raw data by filtered back projection with a Butterworth filter, with a cut-off frequency of 0.5 and order of 10 in the rest and stress studies.

All patients and control group participants underwent echocardiography 3-7 days after gated MPS. Ejection fraction (EF) and regional wall motion of the left ventricle were assessed by m-mode and two-dimensional echocardiography. CTCA was performed on patients for whom ischemia or infarct was identified by gated MPS.

Visual and Quantitative Evaluation

All images were interpreted blindly and separately by two experienced nuclear medicine physicians. The results of MPS with Tc-99m MIBI were classified into four types, including normal, persistent perfusion defects (defects present in both rest and stress images, resembling MI), reversible perfusion defects (defects present only in stress images, but not in rest images, resembling ischemia) and reverse reperfusion pattern (defects seen in the rest images, but not present in the stress images). Regional wall motion abnormalities (hypokinesia or akinesia) and wall thickening problems of the segments of the left ventricle, particularly in the walls for which ischemia or infarct was found by MPS, were assessed visually in gated images by the 4D-MSPECT process program. EF was also calculated.

Statistical Assessment

The Mann-Whitney U test was used to compare the statistical means of EF values and plasma Hba1c levels between the patients who had perfusion abnormalities in MPS or hypokinesia in echocardiography and the patients who had no perfusion abnormalities and no wall motion problems. This test was also used to compare the EF values between group A and group B patients.

The Spearman correlation test was used to evaluate the correlations between age, the risk for CAD, duration of DM, ETT results, perfusion abnormalities in MPS, wall motion abnormalities in both echocardiography and gated MPS, CTCA results and plasma Hba1c levels.

Results

Table 1A and 1B indicate overall findings of anamnesis, Hba1c levels, results of ETT and imaging modalities.

Tc-99m MIBI Gated MPS Findings

There were reversible perfusion defects resembling ischemia in 9 out of 35 group A patients (25.71%) by visual evaluation. There was one persistent perfusion defect resembling MI in addition to ischemia (periinfarct) in one of these nine patients.
(2.85%). All MPS findings in group B participants were normal. The areas of ischemia and infarct were shown in Table 2. In addition to visual evaluation, the segments of perfusion defects were also fixed.

EF values of the left ventricle were calculated by the 4D-MSPECT process program. The mean EF value in group A was 67.85 ± 7.96%. The mean EF value of 9 patients in group A who had ischemia or infarct in MPS was 62.5 ± 7.0%. The mean EF value of the remaining 26 patients who had no perfusion abnormalities in group A was 69.7 ± 7.5%. The mean EF value of 3 patients in group A who had hypokinesia in gated MPS was 54.66 ± 7.02%. The mean EF value of the remaining 32 patients in group A who had no wall motion abnormalities was 68.93 ± 7.21%. The mean EF value in group B was 65.42 ± 5.34%.

Echocardiography Findings
Diastolic dysfunction in echocardiography was noted in 9 patients from group A (25.71%). These 9 patients were the ones who had perfusion abnormalities by MPS. EF values were also calculated with echocardiography. The mean EF value in group A was 72.46 ± 4.95%. The mean EF value of the 9 patients in group A who had ischemia or infarct by MPS as well as diastolic dysfunction by echocardiography was 63.0 ± 4.1%. The mean EF value of the remaining 26 patients in group A who had no perfusion abnormalities by MPS or functional abnormalities by echocardiography was 66.2 ± 5.5%.

The mean EF value of 3 patients in group A who had hypokinesia by gated MPS as well as echocardiography was 60.66 ± 3.78%. The mean EF value of the remaining 32 patients in group A who had no wall motion abnormalities was 68.33 ± 5.0% echocardiographically.

CTCA Findings
The CTCA findings in 9 patients from group A who had ischemia or infarct by MPS were as follows: one-vessel coronary artery disease in LAD was found in 3 patients (33.3%) and two-vessel disease (LAD + RCA) was found in 1 patient (11.1%). One of these nine patients was normal, and the remaining four patients could not be evaluated optimally because of technical problems such as movement artifacts.

Biochemical Results
The mean value of Hba1c levels in group A patients was 9.39 ± 2.37%. The Hba1c level was normal in only one patient (2.85%) and it was above normal in the remaining 34 patients (97.15%) in group A. No statistical difference was found between the mean value of Hba1c levels of 9 patients from group A who had ischemia or infarct by MPS and the remaining 26 patients. The difference between the mean value of Hba1c levels in the 3 patients from group A who had wall motion abnormalities (hypokinesia) by gated MPS and the 26 patients in group A who had no perfusion or wall motion abnormalities was also not statistically significant.

The mean EF value of 9 patients who had ischemia or infarct by MPS was found to be low and statistically significant when compared to the remaining 26 patients in group A, assessed by MPS (P=0.001) and echocardiography (P=0.027).

The mean EF value of the 3 patients who had hypokinesia by gated MPS was also found to be low and statistically significant when compared to the remaining 32 patients in Group A, assessed by MPS (P=0.014) and echocardiography (P=0.046).

The mean EF value of the 9 patients who had perfusion abnormalities by MPS was found to be significantly low when compared to the normal volunteers in group B, assessed by MPS (P=0.001) and with echocardiography (P=0.007).

The mean EF value of the 3 patients who had hypokinesia by gated MPS was also found to be low and statistically significant when compared to the normal volunteers in group B, assessed by MPS (P=0.01) and echocardiography (P=0.037).

No statistical difference was found between the mean values of the 26 patients who had no perfusion abnormality in group A and all of the normal volunteers in group B, assessed by MPS (P=0.068) and echocardiography (P=0.196).

Discussion
CAD is one of the main reasons for mortality and morbidity in patients with DM. CAD is seen in more than half of diabetic patients. It is more frequent in diabetic patients with silent myocardial infarction, and the latest studies suggest that SMI is closely related with increased mortality. Although CAD is the main reason for morality, it is generally asymptomatic and patients have high risk of sudden death, heart failure or acute MI [8]. Because of its high risk for mortality, it is very important to detect CAD in patients with DM early, especially with noninvasive methods [4, 5]. According to recent studies, no single test can supply enough information to detect SMI in asymptomatic patients with type 2 diabetes.
Table 2. Areas of Ischemia and Infarct

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>Areas of Ischemia and Infarct in MPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>M</td>
<td>Inferior and Inferoseptal Ischemia</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>F</td>
<td>Infraapical Ischemia</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>F</td>
<td>Ischemia in Septum</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>F</td>
<td>Ischemia in Septum</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>M</td>
<td>Anteroseptal and Apicoseptal Ischemia</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>F</td>
<td>Anteroapical and Anteroseptal Ischemia</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>F</td>
<td>Ischemia in Septum</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>M</td>
<td>Inferior and Inferoseptal Ischemia</td>
</tr>
<tr>
<td>9</td>
<td>58</td>
<td>M</td>
<td>Anteroapical Infarct, Anterobasal Periinfarct</td>
</tr>
</tbody>
</table>

DM [11-13].

Recently, Tc-99m MIBI MPS studies using a gated technique have become a preferred application. Gated MPS is a technique in which both perfusion and cardiac functions can be evaluated simultaneously. Imaging of regional and global wall motions, wall thickening and ventricular functions can be imaged with this technique. Additionally, some parameters, such as ventricular volumes and EF, can be calculated [12]. We also preferred the Tc-99m MIBI gated MPS technique to evaluate myocardial perfusion and left ventricular functions together.

Wingard et al. indicated that 1/3 of insulin-dependent diabetics (IDDM) die because of CAD and 50% of non-insulin-dependent diabetics (NIDDM) die because of vascular diseases. They found low plasma HDL levels, high triglyceride levels and normal LDL levels in adults with NIDDM in the same study [3]. In our study, plasma triglyceride and LDL levels were high and HDL levels were normal in patients who were shown to have perfusion abnormalities in MPS.

Kumar et al. have demonstrated that MPS is a useful test to diagnose SMI in diabetic patients with hyperlipidemia, hypertension, smoking and familial CAD history. These investigators suggest that CAD should be evaluated in diabetic patients even if they do not have angina-like chest pain because of its high correlation with SMI [14].

Because of its high sensitivity and specificity, MPS is one of the first step non-invasive tests used for patients with DM. It is even possible that MPS could be used together with CA in symptomatic diabetic patients [15].

In a study with 203 type 2 diabetic patients, Janand-Delenne et al. indicated that 15.7% of the patients had functional SMI as shown by ECG and MPS, but coronary artery stenosis was confirmed only in 9.3% of the patients. It was revealed in previous studies that this proportion varies between 9.57%. This wide range is possibly related to mean age, duration of DM, existence of high-risk potential for CAD, presence of SMI or presence of symptoms of CAD in different study populations [16-20].

In the present study, the perfusion abnormality rate was 25.71% with Tc-99m MIBI gated MPS. Reversible perfusion defects (ischemic areas) were found in 9 of 35 type 2 diabetic patients (25.71%) in group A. One of these patients also had an irreversible defect (infarct area). The results of our study are concordant with previous results.

Al-Attar et al. noted that diastolic dysfunction in echocardiography might indicate SMI in a diabetic population. They also proposed that ETT could be used to show myocardial ischemia in asymptomatic type 2 diabetics. They found myocardial ischemia in 3 of 42 patients (7.1%) and abnormal ECG findings in 2 of 42 patients with Tc-99m MIBI MPS. When 11 patients who had ischemic patterns in ETT were evaluated, diastolic dysfunction by echocardiography was shown in 5 patients (45.5%), reversible perfusion defects by MPS was shown in 2 patients (18.2%), and an ischemic pattern by ECG was indicated in 1 patient [21].

ST segment depression was found by ETT in 4 of 9 patients (44.4%) who had perfusion abnormalities in Tc-99m MIBI gated MPS in our study. Diastolic dysfunction of the left ventricle was seen in echocardiography in all 9 patients with perfusion abnormalities.

There was a statistically significant correlation between ischemia (reversible perfusion defects) and duration of DM, ischemia and the risk for CAD (all patients with perfusion defects were in group A), ischemia and CTCA results, ischemia and wall motion abnormality, ETT results and the risk for CAD, wall motion abnormality and the risk for CAD. We could not find a significant correlation between the risk for CAD and duration of DM in this study, although it has been shown previously.

The prevalence of ischemia was found to be 5.29% by Koistinen et al. They proposed that TI-201 MPS after exercise or dipyridamole stress test was more sensitive and specific than ETT alone and routine ECG [22].

In a study with TI-201 MPS, Inoguchi et al. showed that the SMI rate was high in patients with NIDDM over 60 years old. They stated that TI-201 MPS was more sensitive (80%) and specific (87%) than ETT and other diagnostic methods of CAD. The positive predictive value was found to be 94% when ETT and TI-201 MPS were used together. They concluded that using ETT and TI-201 MPS together was very successful in diagnosis of SMI in patients with type 2 DM. The prevalence of SMI in type 2 diabetic patients was found to be 26.3% in a study by Inoguchi et al. [23].

De Lorenzo et al. found positive Tc-99m MIBI MPS findings in 26% of type 2 diabetic patients who had no suspicious cardiac symptoms or history of CAD. In the same study, the rates of ischemia (reversible defect), infarct (fixed defect), and both ischemia and infarct were 15%, 5% and 6%, respectively [24]. De Lorenzo et al. revealed that MPS and Tc-99m MIBI together were more sensitive and specific than ETT in diagnosis of CAD [24].

In our study, we found ischemia in 9 patients (25.7%) and both ischemia and infarct in 1 patient (2.85%) with MPS in group A asymptomatic diabetics. ST segment depression was determined in 4 of these 9 patients in ETT. In the present study, MPS is revealed to be better than ETT at detecting myocardial ischemia in asymptomatic type 2 diabetics, parallel to the study...
of De Lorenzo et al. Yamasaki et al. found wall motion abnormalities (hypokinesia) in 9 of 24 type 2 diabetic patients who had ischemia in Tc-99m MIBI gated MPS. They demonstrated that left ventricle EF was lower in patients with hypokinesia than in patients with no wall motion abnormality [25].

Al et al. and Bloomgnard et al. showed that myocardial ischemia was more frequently seen in diabetic patients and that it was an expected long-term complication of DM [26, 27]. We also found a significant correlation between the duration of DM and reversible perfusion defects (ischemia) in MPS (P<0.025). CAD due to DM is an expected long-term result because of the high potential of diabetic complications.

To evaluate coronary vessels, we tried to perform CTCA in 9 patients whom perfusion defects were diagnosed by MPS, because CTCA is a non-invasive method and the sensitivity (92%) and specificity (93%) are very close to CA. However, we were able to perform CTCA optimally in only 5 of these 9 patients. We were not successful in 4 patients because of technical problems. Although this is a limitation of our study, it is well known that the sensitivity and specificity of Tc-99m MIBI gated MPS in the diagnosis of myocardial ischemia are 90% and 93%, respectively. These rates are very close to the percentages of sensitivity and specificity obtained in CA. Additionally, CA is an invasive method, and CTCA is a noninvasive but more difficult method than gated MPS, which was why we were not able to apply one of these angiographic methods to all patients in our study. However, we think it is meaningful to determine the status of coronary arteries by CTCA in patients with perfusion defects, although the assessment is very difficult to perform optimally.

In conclusion, Tc-99m MIBI gated MPS is a successful, reliable and noninvasive method in the diagnosis of SMI and CAD in type 2 asymptomatic diabetic patients. Further studies in which Tc-99m MIBI gated MPS and CTCA are used together to evaluate CAD in diabetic and non-diabetic patients will be useful for understanding details about cardiac complications of IDDM.

Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

References

24. De Lorenzo A, Lima RS, Siqueira-Filho AG,

