SPECT in Asymptomatic Diabetics with and without Microalbuminuria


Abstract

Objective: To identify coronary artery disease (CAD) in asymptomatic diabetics with the help of myocardial perfusion single photon emission computed tomography (MPS), a non-invasive imaging modality and its correlation in diabetics with or without microalbuminuria.

Methods: This study included 99 patients in the age group of 30 to 80 years who were asymptomatic but possessed one or more risk factors for CAD. These patients were divided into two groups, diabetics with and without microalbuminuria (Micral). Thirty eight patients were Micral positive and 61 were Micral negative. Ischemia was detected by MPS and compared with coronary angiographic findings in both the groups.

Results: Amongst the 99 diabetic patients, MPS was positive in 39 patients. Out of 39 MPS positive patients, 31(79.5%) were micral positive and 8 (20.5%) were micral negative. Out of 38 micral positive patients, 31 patients were positive on MPS and 27 had significant angiographic (CAG) findings. Those with micral positive and MPS positive had multivessel CAD by CAG. It was seen that MPS status was 91.4% sensitive, 74.1% specific and had 82.1% positive predictive values (PPV) and 87.0% negative predictive value (NPV) for detection of significant CAD.

Conclusion: Microalbuminuria is an inexpensive screening tool and a powerful independent predictor for major cardiovascular events in patients with type 2 diabetes mellitus. MPS is a sensitive, non invasive diagnostic test for identification of CAD in asymptomatic diabetic patients.

Introduction

Type 2 Diabetes mellitus (T2DM) constitutes about 85% to 95% of all diabetes cases. Individuals with diabetes have a 2-4 fold increased risk of subsequent cardiovascular disease (CVD) which remains the most important cause of mortality, morbidity and 5 to 10 years reduced life expectancy compared to non diabetics. Several factors lead to accelerated atherosclerosis in diabetes including hyperglycemia, insulin resistance, abnormal lipid profile, oxidative modification of lipoproteins, increased blood pressure and altered fibrinolysis. The prevalence of silent ischemia among asymptomatic diabetics is very high, ranging from 20 to 50%.

Myocardial perfusion single photon emission computed tomography (SPECT) is most useful and highly dependable noninvasive test to diagnose ischemia in asymptomatic diabetics. We have reported abnormal myocardial perfusion scans in 43% of asymptomatic diabetics in our series. In T2DM, microalbuminuria is the earliest clinical sign of vascular damage, which is reflective of generalized vascular damage and systemic vasculopathy. Screening for microalbuminuria is one of the most important simple clinical tools for identifying such patients.

As shown by the Diabetes Control and Complications Trial, intensive treatment of diabetes with improved glycemic control reduces the risk of diabetic complications and delays or prevents the onset of microalbuminuria and results in cardiovascular protection. Microalbuminuria correlates strongly with short-term (5-year) cardiovascular mortality and also predicts onset of congestive heart failure (CHF).

Present study is conducted to identify coronary artery disease (CAD) in asymptomatic diabetics with help of myocardial perfusion study (MPS), a non-invasive imaging modality.

Materials and Methods

This study included ninety nine patients (62 males, 37 females), in the age group of 30 to 80 years who were asymptomatic for CAD, referred for MPS. These patients were divided into two groups – diabetics with microalbuminuria (n = 38) and diabetics without microalbuminuria (n = 61).

Inclusion criteria

Asymptomatic patients of T2DM (fasting blood sugar more than 126 mg/dl or patients on anti-diabetic drugs) with one or more risk factors for CAD.

Exclusion criteria

1. History of angina or equivalent symptoms (the Rose questionnaire)
2. Diabetics with a prior history of ketoacidosis (type 1).
3. Symptomatic patients with history of myocardial infarction.
4. Evidence of renal insufficiency (serum creatinine > 1.5 mgs)
7. History of urinary tract infection 3 months prior to the study.

At study entry, detailed history of the patients along with physical examination and baseline investigations including resting electrocardiogram and echocardiograms were done. All patients underwent MPS and urine evaluation for microalbuminuria (micral).
Protocol for MPS

After explaining the procedure informed consent was taken.

Method

1. Siemens’ ECAM - a dual head variable angle gamma camera
2. Parallel hole collimator (low energy, high resolution)
3. 10 mCi of ⁹⁹ᵐ Tc MIBI at rest and 30 mCi of ⁹⁹ᵐ Tc MIBI at peak stress, intravenously.

Rest protocol

Patients were administered 10 mCi of Tc⁹⁹m MIBI intravenously at rest. SPECT imaging was done 60 minutes post-injection.

Stress Protocol with Adenosine Stress

This was chosen in subjects with physical inability to do exercise like arthritis, post-knee replacement surgery, patients on pacemaker, left bundle branch block. Bronchial asthma was excluded prior to the test. Tea, coffee and medications like dipyridamole and theophylline were discontinued 24 hours before the study. After four hours of rest, injection 30 mCi of ⁹⁹ᵐ Tc MIBI was administered at the third minute of adenosine stress that was infused at a rate of 140 mcg/kg/min for a total of six minutes. Stress ⁹⁹ᵐ Tc MIBI SPECT was done 60 minutes after injection of tracer.

Stress Protocol with Physical Stress

Anti-ischemic medications were discontinued before exercise testing [Betablockers (48 hours), Calcium channel blockers (24 hours) and nitrates (6 hours)]. Either Treadmill exercise or bicycle ergometer was used. Heart rate and blood pressures were recorded at the beginning and at the end of physical stress. Twelve lead ECG was recorded at 3 minute intervals of exercise. The exercise end points included physical exhaustion, severe angina, dysrhythmia or hypotension. 30 mCi of Tc⁹⁹m MIBI was administered at the target heart rate for the patient’s age (85% of maximal heart rate).

SPECT Acquisition Protocol

MPS was performed on dual head scintillation camera using 76-degree acquisition, with 64 projections at 20 seconds per projection. For ⁹⁹ᵐ Tc MIBI, a 20% window centered on the 140 KeV peak was used and images were obtained in supine positions. Gated SPECT was performed obtaining 8 frames/cycle for 180 degree with continuous step and shoot method from 45 degree right anterior oblique (RAO) to 45 degree left posterior oblique (LPO). Images were acquired using 64X64 pixel matrix. Siemens cardiac SPECT reconstruction software program was used. A standard filtered back projection using Butterworth filter order 5 was used. Short axis (axial), horizontal long axis (coronal) and vertical long axis (sagittal) images were obtained.

Image Interpretation

The images were interpreted by two experienced observers independently. A perfusion abnormality at stress, which showed complete filling up at rest, was considered to represent ischemia. A perfusion abnormality that remained unchanged at stress and at rest was considered as fixed defect or scar. The study was considered as normal when there was no demonstrable perfusion abnormality.

Based on the size of perfusion defects [quantified for size as percentage of the left ventricular myocardium as small (<5%), moderate (5-10%) and large (>10%)], the MPS scans were interpreted as follows:
1. Normal stress perfusion study
2. Stress induced or fixed perfusion defects of small size
3. Stress induced or fixed perfusion defects of moderate or large size

All the MPS positive patients were subjected to invasive coronary angiography (CAG) while amongst the 60 MPS negative patients 23 had angiography done. The angiograms were independently interpreted by two experienced cardiologists. A stenosis of greater than or equal to 50% diameter stenosis was considered significant (Figures 1a and 1b).

On the basis of findings of MPS, CAG and micral detection, patients were divided into three groups (A, B and C). Amongst those three groups, cardiovascular risk stratification was done and patients were advised further management.

Urine Micral Evaluation

Early morning first urine sample after an overnight fast was collected and analysed by immunoturbidimetric assay for quantitative determination of albumin. The method for screening for microalbuminuria was by spot urinary albumin determination. A value of more than 20 mg/L was taken as positive for microalbuminuria. Patients were divided into microalbuminuria positive and microalbuminuria negative groups.

Statistical Analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis...
Results

We analyzed 99 diabetic patients who were prospectively evaluated and divided into two groups-diabetics with microalbuminuria (Micral positive) and diabetics without microalbuminuria (Micral negative). The mean age of the study population was 52.7 years. Thirty eight patients were micral positive and 61 were micral negative. Thus the prevalence of micral was 38.38% (Table 1).

Amongst the 99 diabetic patients, MPS was positive in 39 patients. Out of 39 MPS positive patients, 31 (79.5%) were micral positive and 8 (20.5%) were micral negative. The extent of narrowing of coronary vessel on angiography and MPS are shown in Table 2.

It was seen that MPS status was 91.4% sensitive, 74.1% specific and had an 82.1% positive predictive value (PPV) and 87.0% negative predictive value (NPV) for detection of significant CAD.

On comparing the diagnostic efficacy of MPS in micral positive and negative patients separately we found that, out of 38 micral positive patients, 31 patients were positive on MPS and 27 had significant CAG findings. Two patients with negative MPS had significant angiographic findings. Hence 29 (76.31%) out of 38 micral positive patients had significant CAG findings. The correlation between MPS and CAG in patients with positive micral was significant (p<0.001). MPS in detecting presence of CAD in micral positive population showed sensitivity of MPS as 93.10% and specificity of 55.55%. In micral negative patients, out of 24 patients, 8 had positive MPS amongst whom 5 had significant CAG findings. The correlation between MPS and CAG in micral negative patients was significant (p<0.01). MPS was comparatively less sensitive in micral negative subjects in detecting presence of CAD (sensitivity 83.33%); still it was more specific in ruling out significant CAD (NPV 93.75%).

Amongst the MPS positive patients, we found that patients with positive micral had significant CAG findings with multivessel (extensive) disease (p<0.001) as shown in Table 3. Overall in 39 MPS positive patients, we found total 57 perfusion defects involving different arterial territories. Of these, 36 perfusion defects were reversible while remaining was fixed. We found only 5 large defects and rest 52 defects were either small or moderate sized. Of the micral positive subjects approximately 90% had moderate to small perfusion defects.

Discussion

In T2DM, microalbuminuria is a hallmark of microvascular damage and so is an indicator of atherosclerosis. Deckert et al proposed in the Steno hypothesis that impaired vascular endothelial function results in vascular leakage of albumin. Stenhouver and Smulders reviewed the potential relation among endothelial function, microalbuminuria and CAD. Overall prevalence of CAD amongst diabetics in a study by Ignasi Castella et al was 37% which was seen as an abnormal MPS among the diabetics. The presence of microalbuminuria increased the relative risk for the primary end points (myocardial infarction, stroke, or CV death) in subjects with diabetes. Knut Borch-Johnsen et al, in a study proposed that microalbuminuria is a predictor of the development of CAD and also that the CVD risk associated with conventional risk factors was more than doubled when microalbuminuria is present. Data by Gerstein et al suggests that measurement of urinary albumin may help estimate the absolute risk of experiencing a cardiovascular event for individuals with T2DM. Therefore, a test that identifies high-risk patients provides useful information that will help clinicians estimate the benefits that may be expected from adding a proven preventive therapy. In our study also microalbuminuria correlated with positive MPS indicating the presence of CAD.

Several studies have confirmed the high sensitivity of MPS
for the detection of a critical stenosis in patients with known or suspected CAD (sensitivity being 85-90%). Rajagopalan et al\(^\text{17}\) found abnormal SPECT in 59% of asymptomatic diabetics. In our study of asymptomatic diabetics, we reported abnormal perfusion scans by myocardial SPECT in 43% cases compared to 11% in controls.\(^6\)

In this prospective analysis we found high incidence of CAD (81.6%) among the micral positive patients compared to micral negative diabetics. So our study confirms the strong correlation between detection of micral and incidence of CAD in asymptomatic diabetics. In this study we found that myocardial ischaemia was four time more common in patients with microalbuminuria. Similar findings were observed by James Meigs et al, as their study showed that microalbuminuria was associated with a 2.3-fold increased risk of CAD compared with those without micral.\(^18\)

In a study by Jager et al,\(^2\) among 503 Type 2 diabetic subjects followed for 10 years, 2% died from uremia whereas 56% died from cardiovascular disease. In other words, many T2DM subjects die of cardiovascular disease before renal failure develops. Thus, screening for microalbuminuria among T2DM subjects should be used primarily as a means to detect risk of cardiovascular disease.

We divided the patients into three groups according to the results of MPS, CAG and micral. In Group A patients, MPS was negative but CAG was significant which can be explained on the basis of collateral circulation in those patients because of which MPS was negative. With collateral coronary circulation, between 28 and 50% of silent coronary occlusions in humans are not accompanied by a left ventricular dysfunction, suggesting that the presence of pre-existing collateral circulation may protect the myocardium.

In group B, micral was negative but other parameters were positive. Group B patients mostly had single vessel disease and provocable defects as compared to group C who had large and more fixed defects and multivessel disease by angio. Group C patients with all the three parameters being abnormal were at highest risk for cardiovascular events. These patients are potential candidates likely to have major cardiovascular events and must be treated aggressively. It is evident that on the basis of clinical predictors of risk, patients can be categorized as having minor, intermediate or major predictors. A high-risk scan is an indication for early coronary angiography. Rajagopalan\(^\text{17}\) showed in sixty-one percent of patients with a high-risk scan who underwent coronary angiography had high-risk anatomy. Patients predicted to be at high risk by MPS did in fact have a high annual mortality rate of 5.9%. Patients predicted to be at low risk did have a significantly lower but nonetheless substantial annual mortality of 3.6%.

Patients with a high absolute risk will experience a higher absolute risk reduction when given preventive interventions than patients with a lower absolute risk. Therefore, a test that identifies high-risk patients provides useful information that will help clinicians estimate the benefits that may be expected from adding a proven preventive therapy. Albuminuria is an easily measured marker which may be an expression of existing endothelial dysfunction that likely reflects underlying macro vascular and micro vascular disease.\(^10\)

**Conclusion**

Microalbuminuria is an inexpensive screening tool and a powerful independent predictor for major cardiovascular events and all-cause mortality in patients with T2DM and represents early generalized vascular disease.

MPS is a sensitive diagnostic test for identification of CAD in asymptomatic patients with T2DM with microalbuminuria and offers a non-invasive approach for risk stratification in these patients so that necessary intervention and aggressive management can be executed on time.

MPS is a reliable and reproduced test and serves as a prognostic indicator for any cardiac events in patients with T2DM with microalbuminuria.

**References**


