INCIDENCE OF CORONARY ARTERY DISEASE IN PROPENSITY MATCHED DIABETICS AND NON-DIABETICS USING MYOCARDIAL PERFUSION IMAGING AND ITS CORRELATION WITH CORONARY ANGIOGRAM

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ABSTRACT

BACKGROUND: Current guidelines consider diabetes per se as a coronary artery disease (CAD) risk equivalent. Myocardial Perfusion imaging (MPI) has been considered as a powerful non-invasive tool for diagnosing significant CAD. Aims of this study were to detect the incidence of CAD in propensity matched diabetics and non-diabetics by using MPI and to correlate perfusion abnormalities on MPI with coronary angiogram. **MATERIAL & METHODS:** Total 197 patients were included, 142 (72%) males and 55 (28%) were females, aged between 32 to 74 years (mean age = 58.5, median age =57 years). 92/197 diabetic patients were labeled as group A while remaining 105/197 non-diabetic were labeled as group B. Patients with prior myocardial infarction (MI) or revascularization were excluded. All included patients were subjected to MPI by using Tc^{99m} Methoxy Isobutryl Isontrile (MIBI) with one day stress protocol. Coronary angiogram was done one month prior or after a positive MPS. **RESULTS:** Both groups were statistically similar in age, sex, weight and non-modifiable risk factor like positive family history of CAD. While hypertension and dyslipidemia was significantly higher in diabetics as compared to non-diabetics (83%:65% and 64%:36% respectively; $p<0.05$). The incidence of CAD as detected by perfusion defects on MPS was significantly higher in diabetics than non-diabetics (51% Vs 31%; $p<0.05$). Coronary angiography was available in 103/197 patients and calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in diabetics versus non-diabetics were 97.9%:84.6%, 44.4%:71.4%, 90.4%:94.3%, 80%:45.5% and 89.5%:82.6% respectively. Sensitivity and NPV was significantly higher in diabetics and specificity was higher in non-diabetics ($p <0.05$) while accuracy and PPV was statistically similar in both groups. In diabetics there was significantly higher ischemic burden (reversible perfusion defects 37% and transient ischemic dilation TID 18%; $p<0.05$) with predominance of multi-vessel involvement of 43% ($p<0.05$). **CONCLUSIONS:** The incidence of CAD on MPI is significantly higher in diabetic than propensity matched non-diabetics. MPI is more sensitive but less specific for CAD in diabetics but has a comparable accuracy for both groups. Diabetics are more prone to have significant higher ischemic burden than non-diabetics.

Key words: Diabetes Mellitus; myocardial perfusion imaging; coronary angiography and coronary artery disease

Introduction

Diabetes mellitus (DM) is one of the most important diseases in modern society and has been considered as the major medical and social problem. The prevalence of DM has been on a rise and it is speculated that about 366 million people will be affected by 2030.[1] DM has been proclaimed by world health

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organization (WHO) as an equivalent to coronary artery disease (CAD). According to WHO data more than 75% of patients with type 2 DM die due to cardio-vascular events.[2] Myocardial perfusion imaging with single photon emission computed tomography (MPI-SPECT) is a well established non-invasive tool for diagnosis, prognosis and risk stratification in DM and non-DM.[3] The MPI has a reported prevalence of ischemia varying from 17%-59%.[4] However results of the recent DIAD study (Detection of Ischemia in Asymptomatic Diabetics) shows a prevalence of myocardial ischemia 22% and concludes that MPI is not justified in asymptomatic diabetics for screening.[5] Coronary angiogram is still considered as gold standard for diagnosis of CAD, however in diabetic small vessel disease and endothelial dysfunction with non-obstructive epicardial vessels with positive MPI has become a mater of debate in recent years.

Aims of the study were to find out the incidence of CAD in propensity matched diabetics and non-diabetics by using MPS and to correlate perfusion abnormalities on MPS with coronary angiogram.

Material and Methods

This is a prospective study conducted at Nuclear Cardiology Department of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, Pakistan from September 2011 till January 2012. The study was duly approved by the ethical committee of the institute. Total 197 age and sex-matched diabetics and non-diabetics with or without associated risk factors referred for diagnosis or risk stratification were included. Patients with prior MI, history of revascularization (CABG/PCI) or non-ischemic ischemic heart disease were excluded.

Study Population: Out of 197 patients, 92 (47%) diabetics with mean age of 59 ± 9.58 years (Male: Female 65:27) were labeled as group A. Remaining 105 (53%) with mean age of 58 ± 12 years (Male: Female 77:28) non-diabetics were labeled as group B. In Group A, risk factor assessment revealed that hypertension (HTN), dyslipidemia (DYSLIP), positive family history (F/H) and history of smoking (SMK) was found in 83%, 64%, 52 and 26% patients respectively. While in Group B, HTN, DYSLIP, F/H and SMK was found in 65%, 36%, 49% and 29% respectively (Tab.1).

Variables	Diabetics (92) Group A	Non-Diabetics (105) Group B	Statistical Test Value	p-values
Age (mean ± SD) yrs	59 ± 9.58	58 ± 12	-0.663 (t-test)	0.572
Gender				
Male	65 (71%)	77 (73%)	0.234 (χ^2)	0.878
Female	27 (29%)	28 (27%)		
Weight (Kg)	71 ± 16	67 ± 15	-1.810 (t-test)	0.072
Risk Factor				
HTN	76 (83%)	68 (65%)	7.243 (χ^2)	0.007*
DYSLIP	59 (64%)	38 (36%)	14.283 (χ^2)	0.0002*
F/H +	48 (52%)	51 (49%)	0.076 (χ^2)	0.782
SMOKER	24 (26%)	30 (29%)	0.092 (χ^2)	0.756
Stress protocol				
Bruce	65 (71%)	79 (75%)	0.222 (χ^2)	0.638
Persantin	27 (29%)	26 (25%)	0.222 (χ^2)	0.638
MPHR	86 ± 9	87 ± 10	0.734 (t-test)	0.464
METs	7.37 ± 2.28	7.88 ± 2.05	1.653 (t-test)	0.099

*p<0.05
SD= Standard Deviation
χ^2=Chi-square
HTN=Hypertension
DYSLIP=Dyslipidemia
F/H=Family History for CAD
MPHR=Maximum Predicted Heart Rate
MET=Metabolic Equivalent Task

Table 1: Demographic Characteristics of Patients in both groups

Acquisition Protocol: All patients underwent same day (stress-rest or stress only if normal) myocardial perfusion SPECT using Tc^{99m} labeled Methoxy IsoButyl Isonitrile (MIBI). 07-10 mCi of Tc^{99m} MIBI was administered intravenously for stress and 25-30 mCi for resting study. SPECT acquisitions were performed using dedicated dual head cardiac (Cardio MD, Philips) gamma camera with low energy all purpose (LEAP) collimator, 32 projections around a 180 degree arc, a 64 x 64 matrix. Image reconstruction was done by using commercially available Astonish®. Similarly, SPECT MPI with SSS, SRS and SDS >2 were considered as abnormal.

Stress Protocol: Dynamic exercise and dipyridamole stress were used in 71%: 29% in Group A and 75%: 25% in Group B (Tab.1). Beta blockers, calcium blocker and long acting nitrate were stopped 24-48 hours prior the test. Tea, coffee and xanthine derivatives were stopped 24 prior in patients scheduled for dipyridamole test. The mean target HR (THR) achieved was 86 ±9% in Group A and 87 ±10% in Group B (Tab.1). Pharmacological intervention was performed with 0.567 mg/kg of dipyridamole for 4 minute. Tc-99m MIBI was

given 1 minute before terminating exercise or 3-4 minute after dipyridamole infusion.

Statistical Analysis: Comparisons between patient groups were performed using Student's t test for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean ± standard deviation (SD). Statistical significance was defined as P<0.05. Commercially available packages Medcalc® and statistical package for social sciences (SPSS 17®) were used.

Results

There was incidence of CAD on MPI in diabetic (Group A) was 51% which was significantly higher than non-diabetic counterpart (Group B) of 31% (p value <0.05). (Tab. 2).

Variable	Diabetics (92) Group A	Non-Diabetics (105) Group B	Chi-square value	p-values
MPS findings				
Normal	45(49%)	72 (69%)	7.340	0.0067*
Overall defects	47 (51%)	33 (31%)	7.340	0.0067*
Fixed	11 (12%)	15 (14%)	0.415	0.839
Reversible	34 (37%)	17 (16%)	10.224	0.0014*
Mixed	02 (02%)	01 (01%)	0.0001	0.990
TID	17 (18%)	08 (07%)	4.580	0.0323*

*p<0.05
MPS = Myocardial Perfusion Imaging
TID = Transient Ischemic Dilatation

Table 2: Myocardial Perfusion scintigraphy findings in both Diabetic (group A) and non-Diabetic (Group B)

Coronary angiography was performed in 103/197 patients and it was considered as gold standard. Out of these 103 patients, 57 (55%) were diabetics and 46 (45%) were non-diabetics. A luminal narrowing more than 70% (visually) in any coronary and more than 50% narrowing in left main was considered hemodynamically significant.6 In diabetic cohort MPS was found to have sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of 97.9%, 44.4%, 90.4%, 80% and 89.5% respectively. While in non-diabetics sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy was 84.6%, 71.4%, 94.3%, 45.5% and 82.6% respectively (Tab.3).

	DM	Non-DM	p-value
Total angiograms	57	46	---
True Positive	47	33	---
True Negative	04	05	---
False Positive	05	02	---
False Negative	01	06	----
Sensitivity	97.9%	84.6%	0.0354*
Specificity	44.4%	71.4%	0.0108*
Positive Predictive Value	90.4%	94.3%	0.7166
Negative Predictive Value	80%	45.5%	0.0006*
Accuracy	89.5%	82.6%	0.467
*p-value<0.05			

Table 3: Correlation between MPS and coronary angiography

Sensitivity and NPV was significantly higher in diabetics while specificity was higher in non-diabetics (p <0.05). Accuracy and PPV was statistically similar in both groups (p non-significant) (Tab. 3). There was statistically similar incidence of fixed perfusion defect on MPS in both groups (p=0.839), with significantly higher incidence of reversible perfusion defects of 37% (p<0.05) and transient ischemic dilation 18% (p<0.05) in diabetics (group A) demonstrated in (Fig.1).

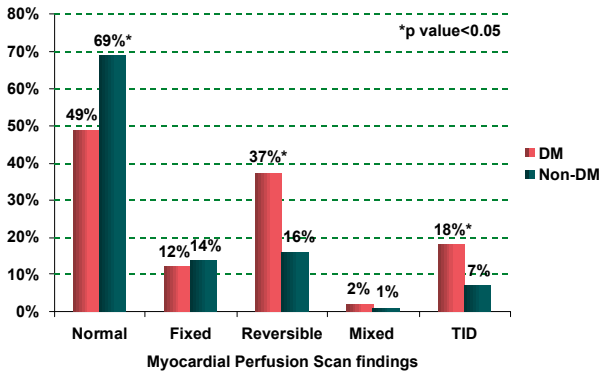

Figure 1: Comparative analysis of myocardial perfusion scan findings in Diabetic (group A) and non-Diabetic (Group B). DM=Diabetics, Non-DM=Non Diabetics, TID=Transient Ischemic Dilatation

While territory wise involvement present on MPS when confirmed with coronary angiogram revealed significantly higher incidence of multi-vessel involvement of 43% in diabetics (group A) as compared to 24% in non-diabetics (group B) while individual Left Anterior Descending (LAD), Right Coronary Artery (RCA) and Left Circumflex Artery (LCx) defects were statistically similar in both groups (Fig. 2). In comparison of size of perfusion defects on MPS, there was significantly higher incidence of large size perfusion defect of 43% (p<0.05) in diabetics (Group A) as

compared to 18% in non-diabetics (group B) while small and medium sized perfusion defects were relatively higher i.e. 30% and 51% respectively in non-diabetics (group B) but statistically non-significant as compared to diabetics (Group A) i.e. 17% and 40% respectively as demonstrated (Fig. 3).

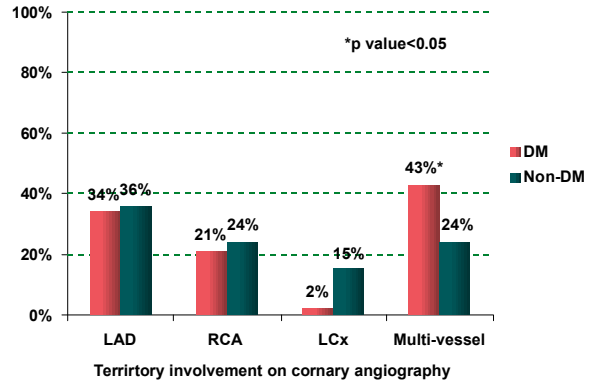

Figure 2: Comparative analysis of territory involvement on myocardial perfusion scan confirmed on coronary angiogram in Diabetic (group A) and non-Diabetic (Group B). DM=Diabetics, Non-DM=Non Diabetics, LAD=Left Anterior Descending, RCA=Right Coronary Artery, LCX=Left Circumflex

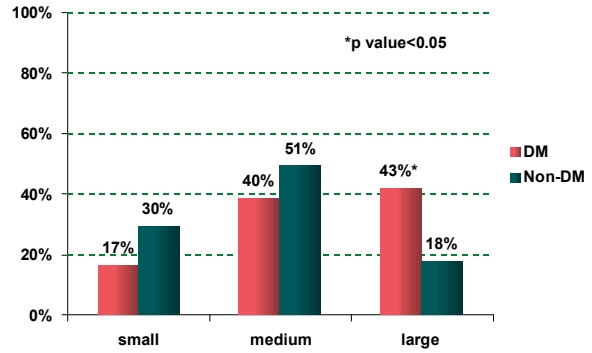

Figure 3: Comparative analysis of myocardial perfusion defects in both Diabetics (Group A) and non-Diabetics (Group B). DM=Diabetics, Non-DM=Non Diabetics, *p<0.05

Discussion

In our study both diabetic and non-diabetics group were propensity matched for non-modifiable risk factors like age, gender, weight, family history which gives statistical strength to the matched cohorts and reduces the chances of biasness. Regarding the modifiable risk factors like hypertension and dyslipidemia were significantly higher in diabetics as compared to non-diabetic group. This can be explained by the association of hypertension and dyslipidemia with deranged insulin metabolism independently of obesity and body weight.[7] Dynamic stress was used in two-third of population in both groups with almost nearly matched functional capacity as indicated by maximum predicted heart rate and metabolic equivalent task (non-significant p value) which is in concordance with a recently published study upon Pakistani male and females.[8] Although this may be regarded as an unexpected observation as diabetics are considered to have relatively low functional capacity due to small vessel involvement in coronary and peripheral vascular beds.[9] This could be explained by male predominance in both groups who are considered to have better functional capacity as compared with females.[10] The other possible explanation could be duration of diabetes (mean 11.56 years) in this study as studies have shown higher incidence (about 45%) of peripheral vascular disease in diabetic at 20 years (15% with 10 year duration of diabetes).[11] However, a study upon Pakistani population has shown a similar effort tolerance in both genders. The incidence of positive MPI in diabetic group was statistically significant higher than non-diabetic cohort (51% Vs 31%; p value<0.05). This is in concordance with most of published studies with reported incidence range of 25-50%.[12,13,14] This is important to mention that our study is a prospective study conducted on propensity matched diabetics and non-diabetics as compared to these published studies which were retrospective. However our incidence is significantly higher as compared to DIAD's.[5] Detection of Ischemia in Asymptomatic Diabetics) and study by Scholte et al.[15] However our incidence is lower as compared with a study published by Elhendy et al.[16] 12% Vs 26%) in diabetics. Interestingly the incidence of reversible ischemia (37% Vs 16%; p value <0.05) was significantly higher in diabetics and this correlated with concomitant multi-vessel disease on coronary angiograms. This incidence is in concurrence with reported incidence of 30% and 35%.[14,15] Transient ischemic dilatation is a recognized predictor of multi-vessel disease with or without involvement of LAD artery. Although exact mechanism is not known; but it is presumed to be due to global sub-endocardial ischemia, systolic dysfunction and LV dilation during end diastole.[17] The incidence of TID in diabetic cohort in this study was 18% (p<0.05) and this correlates with high incidence of multi-vessel disease on coronary angiography. The incidence of TID in this study correlates with reported incidence of 14%.[18,19] and 25%[20] while it is higher than 7%[17] in other published study. The plausible explanation of higher incidence could be biased sampling as we recruited diabetics. Another explanation for this fact

could be higher ischemic burden as indicated by higher precedence of non-fatal MIs in patients with TID.[17] The sensitivity of MPS was significantly higher in diabetics group as compared with non-diabetics cohort (97.9% Vs 84.6% respectively) this value is appreciably higher than reported values.[21] This could be explained by biased sampling, higher incidence of epicardial and small vessel disease, and endothelial dysfunction with normal epicardial vessel in diabetic.[22] The specificity of MPS was significantly high in non-diabetics (71.4%) and this is comparable with the reported values of 70-75% for non-gated MPS.[23] The reason for low specificity i.e. 44.4% in diabetic population is relatively high false positive results. This is an important observation and has been a point of debate whether these are truly false positive in view of non-obstructive CAD or true positive due to impaired coronary flow reserve with small vessel disease in diabetics as has been observed in PET perfusion studies. There is growing evidence that MPS may be more sensitive than coronary angiography to detect critical stenosis in patients with diabetes. Given that patients with diabetes and no evidence of CAD have a risk of myocardial infarction similar to that of patients with a history of myocardial infarction,[24] the finding of a reversible myocardial perfusion defect in a diabetic patient without obstructive CAD may reflect ano- malies in the coronary vasodilator function induced by diabetes.[25] PPV was statistically similar in both groups (90.4% and 94.3% in diabetics and non-diabetics respectively) and this is in concurrence with reported incidence.[26] The high predictive values can be explained by epidemiologically biased sampling as we recruited specific population like both diabetics and non diabetics with similar risk factors and furthermore significantly higher prevalence of CAD in both cohorts. The NPV in diabetic group was 80% and this correlates with published value of 86%.[26] This is explained by higher sensitivity of MPS for detecting ischemia in patients with non-obstructive CAD (due to impaired coronary flow reserve). However, in non-diabetic group, the NPV was 45.4% as reported by Scanlon et al.[27] This could be explained by the possibility that these patients might have not stopped beta or calcium blockers which is a known factor for higher false negative results of MPI (although patients were clearly briefed about the pre-test protocol). Another possible explanation could be the higher incidence of balanced ischemia in these patients.[17] Accuracy of MPS was similar in both groups and this coincides with one study which has reported a similar accuracy of MPS in diabetic and non diabetic patients.[28] However, there is growing evidence that MP-SPECT may be more sensitive than coronary angiography to detect critical stenosis in patients with diabetes. Given that patients with diabetes and no evidence of CAD have a risk of myocardial infarction similar to that of patients with a history of myocardial infarction,[29] the finding of a reversible myocardial perfusion defect in a diabetic patient without obstructive CAD may reflect anomalies in the coronary vasodilator function induced by diabetes.[25] Perfusion defects in anterior wall, septum and apex (LAD territory) was the most common scintigraphic pattern observed in both cohorts followed by RCA and LCX territories and this is an established fact about CAD distribution worldwide.[30] However, the incidence of multivessel disease was more common in diabetic group which is an expected finding as diabetic are more prone to have severe and multivessel disease than non-diabetic. Patients with diabetes are at a 2-4-fold greater risk of cardiovascular mortality and are both more likely to have silent ischemia and less likely to survive a myocardial infarction than non diabetic individuals.[22] In our study the incidence of small and medium size perfusion defects on MPS was higher in diabetic than non-diabetic counterpart although statistically non-significant. This may be explained by involvement of non-LAD artery resulting in small or medium size defects. On the other hand the incidence of large size defects was not only higher but significant as well in diabetic. This is well correlated by the higher incidence of multivessel disease (with or without LAD involvement) in diabetic.

Limitations

We do feel that referral bias is a limitation of this study but as a matter of fact our institute is catering about 5 million population of the largest city of country and represents a usual referral in a tertiary care hospital. We did not use gating for SPECT MPI which may be a reason of low specificity in diabetics. This study lacks most of true- and false-negative cases as angiogram was not justified in these patients. We could not follow these patients for clinical outcome due to study duration constraint.

Conclusions

The incidence of CAD on MPI is significantly higher in diabetic than propensity matched non-diabetics.

MPI is more sensitive but less specific for CAD in diabetics but has a comparable accuracy for both groups. Diabetics are more prone to have significant higher ischemic burden than non-diabetics.

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