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Significance of Myocardial Perfusion SPECT (Single-Photon Emission Computed Tomography) Imaging in the Detection of Silent Myocardial Ischemia in Type II Diabetic Patients with Microalbuminuria

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ABSTRACT

Silent Myocardial ischemia is frequent among type II diabetic patients. **Objective:** To evaluate the role of microalbuminuria in predicting silent myocardial ischemia in diabetics undergoing myocardial perfusion scintigraphy and identify a sub-group for early myocardial perfusion scintigraphy and precise coronary artery disease treatment. **Methods:** This prospective study was conducted at the Pakistan Institute of Nuclear Medicine Cancer Hospital, Faisalabad, Pakistan from December 2023 to May 2024. Fifty-four patients were included in the study. All patients were type II diabetics with no previous history of coronary artery disease or angina pectoris. Gated myocardial perfusion scintigraphy was performed in all the subjects. Microalbuminuria was assessed in the morning urine samples of each patient. **Results:** Silent myocardial ischemia was detected in 26 (48%) of the 54 patients. The incidence of silent ischemia was significantly higher ($p<0.05$) in diabetic patients with microalbuminuria 22 (58%) as compared to diabetic individuals without microalbuminuria 12 (75%). Microalbuminuria was the independent and significant predictor of silent myocardial ischemia on myocardial perfusion scintigraphy (odds ratio 6.61, 95% CI 1.23 – 35.38; p=0.027). **Conclusions:** It was concluded that testing for microalbuminuria in asymptomatic type II diabetes patients can improve testing accuracy for detecting silent myocardial ischemia with myocardial perfusion scintigraphy. Myocardial perfusion Single-Photon Emission Computed Tomography scintigraphy (SPECT) is a useful imaging technique for early coronary artery disease detection in individuals with DM.

INTRODUCTION

Coronary artery disease (CAD) is one of the important causes of mortality and morbidity in diabetic patients. Type II diabetics have a two- to four-fold higher risk for CAD in contrast to non-diabetic individuals and they are more susceptible to silent myocardial ischemia (SMI) and poor outcome after a cardiovascular event. Silent myocardial ischemia is a sequel of angiopathy (both microangiopathy and macroangiopathy) which usually starts within 5 years in diabetic patients simultaneously affecting the vasculature of target organs namely kidneys, retina, and cardiovascular system [1]. Target organ damage to kidneys manifests itself as microalbuminuria whereas in the retina manifests itself as retinopathy both of which can be easily determined by simple tests such as urine testing for microalbuminuria and fundoscopic examination for retinopathy [2]. However, target organ damage to the cardiovascular system which manifests itself as myocardial ischemia is usually silent ischemia and therefore remains undetected for a long time till serious complications such as myocardial infarction or sudden cardiac death occur. The occurrence of

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microalbuminuria in diabetic patients suggests that angiopathy has started in the target organs namely kidneys, retina, and cardiovascular system. Therefore, there is a high probability of detecting silent myocardial ischemia due to coronary artery disease (CAD) in these subjects by using myocardial perfusion scintigraphy (MPS) [3]. Several non-invasive techniques have been developed to identify silent myocardial ischemia among diabetics. Among these techniques, myocardial perfusion SPECT imaging offers several advantages such as being non-invasive, relatively low cost, and offering several functional parameters assessment. However further subgroup of patients which will benefit from MPS SPECT scintigraphy is debatable. Several studies have reported microalbuminuria as one of the possible predictors of SMI [4].

This study aimed to detect silent myocardial ischemia among type II diabetics using gated myocardial perfusion imaging, assess risk factors for CAD development in type II diabetics, and analyze the usefulness of microalbuminuria as a predictor of coronary artery disease in asymptomatic type II diabetics.

METHODS

A prospective study was conducted at the Pakistan Institute of Nuclear Medicine, (PINUM) Cancer Hospital, Faisalabad, Pakistan from December 2023 to April 2024. The institutional ethical committee at PINUM Hospital (PINUM-Estt-1(28)/15) approved this study. The empirical technique was used for sample size calculation. 59 patients were included in the previous study [5]. Non-probability convenient sampling technique was used. According to Outpatient Department (OPD) records, patients undergoing stress MPS were 5 per week which makes a total of 160 patients in 6 months. One out of three patients was diabetic and thus sample size for 6 months was Fifty-four (54) individuals in this study. Out of fifty-four patients, 28 were males and 26 were females with an age range from 35 to 80 years and a mean of 55 ± 9 years. These patients were type II diabetics who were referred for MPS from different Diabetic Centers. Study inclusion criteria were patients of both genders with known type II diabetes mellitus and with no previous history of myocardial ischemia. Patients with known CAD, previous history of coronary angiography or coronary artery bypass, history of MI or heart failure, abnormal ECG, second-degree heart block, pregnancy and lactation, and patients with known renal disease other than diabetic nephropathy were excluded. Written informed consent was taken from all patients. Clinical tests included blood and urine samples for microalbuminuria, dyslipidemia, and HbA1c levels. Microalbumin was measured by a quantitative turbidimetric test for the measurement of microalbumin in human urine. Values up to 20mg/L in a first-morning urine specimen were considered normal. Venous samples of every patient included in my study were collected for fasting lipid profile. The reference value for Cholesterol was120-200 mg/dl, High-Density Lipoproteins (HDL) in males 30-65 mg/dl and females 35-80 mg/dl, Low-Density Lipoproteins (LDL) 90-160 mg/dl, Triglycerides to 200 mg/dl. The reference range for HbA1c was 4.8-5.9%. Hypertension was defined as a blood pressure > 140/90 mmHg or normal blood pressure values on antihypertensive drug treatment. A family history of CAD was defined as a diagnosis of CAD in parents or siblings under 50 years of age. Gated Myocardial Perfusion (GMPS) SPECT studies (rest and stress) were performed employing a 2-day protocol. Each study was performed using 99mTc-Tetrofosmin, MyoviewTM, obtained from GE Healthcare Limited, UK. Freshly eluted 99mTc-pertechnetate from 99Mo-99mTc generator (Pakgen-IPD, PINSTECH) was used for labeling of Tetrofosmin for rest and stress GMPS. Stress testing was done by either pure physical stress, pure pharmacological stress, or dual stress (pharmacological and physical). Double-headed Gamma Camera was used for the acquisition of all rest and stress studies. MPI acquisition was done 15 minutes after stress in the stress study and 30 minutes after a fatty meal in the resting study. Gated SPECT acquisition was done using a large field-of-view gamma camera equipped with a low-energy high-resolution parallel hole collimator. Raw data were collected in a 64 × 64 matrix, with a zoom of 1.5, using 60 projections, and an acquisition time of 20 s for each step. The energy set was centred on the 140 keV photo peak of 99mTc with a 20 % window. Iterative reconstruction was the method used for the reconstruction of images. Processing was done by using a Butterworth filter at a cut-off value of 0.52. Gated SPECT images were analyzed by simple analysis of raw data and review of tomograms. Data analysis was done using a statistical package for social sciences (SPSS version 22.0). Patient groups were compared using unpaired Student's t-test for continuous variables and the chi-square test for categorical variables. Percentages for discrete variables and mean ± SD for continuous variables were generated by using descriptive statistics. Binary logistic analysis was used to evaluate the factors predicting silent myocardial ischemia. Family history of CAD, microalbuminuria, HbA1c, hypertension, dyslipidemia, and smoking habits were the only dependent variables considered for logistic regression analysis.

RESULTS

Among the 54 diabetic patients included in our study, 26 (48%) patients had silent myocardial ischemia (SMI) while 28 (52%) patients had no SMI. Only 4 (15.38%) patients had mixed defects. None of the patients was found to have only fixed defects. There were 22 (84.62%) patients who had only reversible defects (Figure 1).

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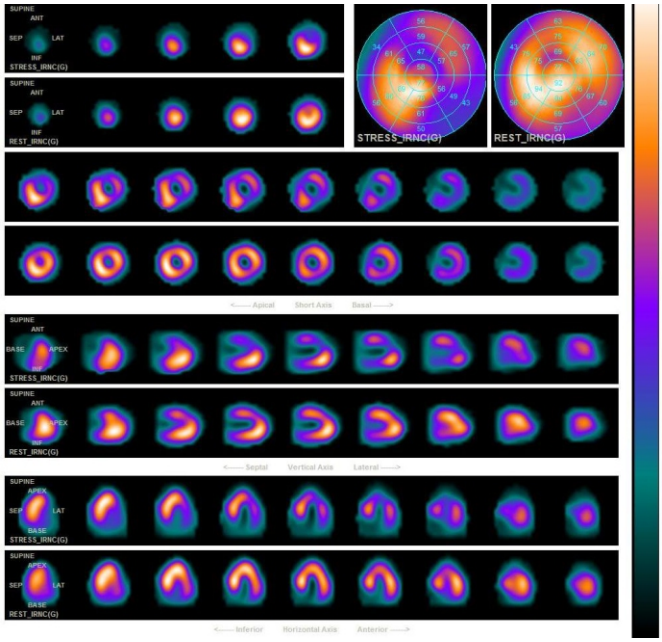

Figure 1: Patients Who Had Only Reversible Defects. 50 yrs Old Male Diabetic for 20 Years, Hypertensive for 1.5 Years and Positive Family History for Ischemic Heart Disease (IHD).

MPS showing mild to marked ischemia involving apex, anteroseptal, anterior, lateral and adjoining inferior walls of LV. Rest-gated SPECT showed normal LV cavity size with adequate LV systolic function and hypokinesia of inferior and anteroseptal walls (Figure 2).

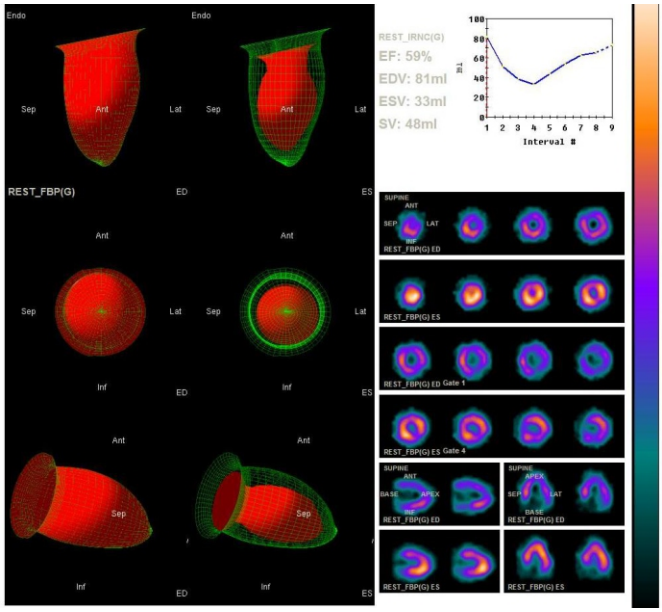

Figure 2: Normal LV Cavity Size with Adequate LV Systolic Function and Hypokinesia of Inferior and Anteroseptal Walls.

When patients with silent ischemia and patients with no ischemia were compared regarding risk factors like age, diabetes duration, dyslipidemia, family history, hypertension, smoking, HBA1c, and diabetes treatment, it was found that patients with SMI were significantly different from patients with no ischemia exclusively for the higher rate of microalbuminuria (84.6% vs. 32.1%, respectively; p=0.027). 9 ischemic patients were smokers while 4 smokers had no ischemia with p=0.080. When ischemic and non-ischemic patients were compared about HbA1c, the p-value was found to be statistically insignificant (p=0.104) (Table 1).

Table 1: Characteristics of Type II Diabetic Subjects Concerning Silent Ischemia

Variables	Ischemia n (%) / (mean ± SD) (n=26)	Without Ischemia n (%) / (mean ± SD) (n=28)	p-value
Age (Years)	55.192 ± 8.404	54.464 ± 10.14	0.776
Gender			
Male	19 (73.1%)	09 (32.1%)	-
Female	07 (26.9%)	19 (67.9%)	
Diabetes Duration (Months)	98.65 ± 95.956	82.785 ± 62.178	0.478
Family History of CAD	10 (38.46%)	07 (25%)	0.2872
Hypertension	17 (65.38%)	16 (57.14%)	0.534
Dyslipidemia	10 (38.5%)	09 (32.1%)	0.627
Smoker	09 (34.61%)	04 (14.29%)	0.080
HbA1c (%)	8.779 ± 2.29	7.718 ± 2.311	0.104
Diabetes Treatment			
Oral Hypoglycemic	19 (73.1%)	22 (78.57%)	0.637
	07 (26.9%)	06 (21.42%)	
Insulin Therapy			
Microalbuminuria	22 (84.6%)	09 (32.1%)	0.027

*Level of significance<0.05.

There was a significantly higher incidence (p<0.05) of silent myocardial ischemia among diabetics with microalbuminuria 22 (58%) in comparison to diabetic individuals with no microalbuminuria 12 (75%) (Table 2).

Table 2: Association of Silent Myocardial Ischemia (SMI) and Microalbuminuria (MAU) in Diabetic Patients (Chi-Square Test; p=0.02)

Microalbuminuria (MAU)	Silent Myocardial Ischemia (SMI)		Total
	Negative	Positive	
Negative	12 (75%)	4 (25%)	16
Positive	16 (42%)	22 (58%)	38

When these patients were assessed further for the risk factors, it was found that age and smoking were statistically significant risk factors among these patients. Four patients had no microalbuminuria but SMI was detected on GMPI. 16 patients were positive for MAU with normal GMPI study (Table 3).

Table 3: Comparison of Variables in MAU +ve & SMI –ve with MAU –ve & SMI +ve Patients

Variables	MAU + ve & SMI –ve n (%) / (mean ± SD) (n=16)	MAU –ve & SMI +ve n (%) / (mean ± SD) (n=4)	p-value
Age (years)	51.13 ± 10.04	61.5 ± 6.95	0.04
Family History	5 (31.25%)	01 (25%)	0.80
Smoking	1 (6.25%)	2 (50%)	0.03
Hypertension	6 (37.5%)	2 (50%)	0.18

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Diabetes Treatment			
Oral	12 (75%)	2 (50%)	0.33
Insulin	4 (25%)	2 (50%)	
HBA1c	8.52 ± 2.52	9.2 ± 2.76	0.67
Diabetes Duration (Months)	97.56 ± 56.99	177 ± 171.49	0.42

*p-value<0.05

Binary logistic analysis was done to ascertain the consequences of HTN, family history, MAU, HBA1c, and smoking in predicting SMI. The regression coefficients of independent variables were positive thus showing a positive relationship between risk factors and SMI. With MAU there were 6.61 times more chances to have SMI. The p-value for HbA1c was found to be borderline (OR 3.98, p=0.05). Only microalbuminuria was independently and significantly associated with the risk of silent myocardial ischemia (OR 6.61, 95 % CI; p=0.027). p-values for other risk factors were found to be statistically insignificant. (Table 4).

Table 4: Table Univariate Binary Logistic Analysis for Factors Predicting Silent Myocardial Ischemia

Factors	Exp (B)=OR	95.0% C.I. for EXP(B)		p-value
		Lower	Upper	
Microalbuminuria	6.61	1.23	35.38	0.027
HbA1c	3.98	0.99	16.01	0.05
Dyslipidemia	1.28	0.31	5.35	0.73
Family History of CAD	0.94	0.22	3.971	0.93
Smoking	3.49	0.68	8.11	0.13
Hypertension	1.96	0.47	8.16	0.35

*p-value<0.05

Patients were also assessed by segregating them into two population groups; one group with SMI and microalbuminuria (n=22) and the second group without SMI and norm albuminuria (n=12). These groups were significantly different concerning HBA1c (p<0.05). Age, gender, diabetes duration, smoking, hypertension, and family history were found to be statistically not significant (Table 5).

Table 5: Characteristics of Patients Having Microalbuminuria with SMI and Norm Albuminuria without SMI

Variables	Microalbuminuria & SMI n (%) / (mean ± SD)(n=22)	Norm Albuminuria & No SMI n (%) / (mean ± SD)(n=12)	p-value
Age	54.5 ± 8.01	58.91 ± 8.78	0.1633
Gender			
Male	17 (77.27%)	06 (50%)	0.104
Female	05 (22.73%)	06 (50%)	
Diabetes Duration (Months)	84.68 ± 73.13	63.08 ± 65.71	0.388
Family History	09 (40.91%)	05 (41.66%)	0.966
Smoker	07 (31.82%)	03 (25%)	0.677
Hypertension	14 (63.64%)	09 (75%)	0.498
Treatment			
Oral	17 (77.27%)	10 (83.33%)	0.676
Insulin	05 (22.73%)	02 (16.66%)	
Dyslipidemia	10 (45.45%)	04 (33.33%)	0.493
HBA1c	8.65 ± 2.17	6.73 ± 1.48	0.0049

*p-value<0.05

DISCUSSION

Coronary artery disease (CAD) and cardiovascular events are highly prevalent among diabetics. CAD is frequently silent, diagnosed at an advanced stage, and is associated with an unfavorable prognosis in diabetics as compared to non-diabetic individuals. [6]. There is a two to four times more chance of silent myocardial ischemia (SMI) in type 2 diabetics than in the general population. Detecting CAD early in high-risk diabetic patients is crucial for improving prognosis, given the challenges of modifying risk factors across large populations due to logistical and financial constraints [7]. Exercise tolerance tests (ETT), stress echocardiography, gated myocardial perfusion SPECT imaging (MPI), coronary angiography, and cardiovascular magnetic resonance (CMR) imaging are various techniques used for screening CAD in asymptomatic diabetic patients. Coronary angiography is the gold standard imaging modality for CAD but due to its invasiveness, ethical concerns, and costs, MPI may be preferred as the initial non-invasive imaging modality for detecting myocardial ischemia [8, 9]. SPECT MPI stands out for its ability to simultaneously detect cardiac perfusion abnormalities and assess left ventricle (LV) parameters including LV volumes (end-diastolic and end-systolic volume), and left ventricular ejection fraction (LVEF), all of which are crucial for prognosis and treatment decisions in cardiac diseases [9]. It has been emphasized to detect subclinical CAD to reduce the probability of cardiovascular events through aggressive management and this improves risk stratification in patients with type II diabetes [9]. Asymptomatic diabetic patients with abnormal resting ECG, peripheral vascular disease, or two or more additional risk factors for CAD (dyslipidemia, hypertension, smoking, positive family history of CAD, and albuminuria) are candidates for screening for CAD [10, 11]. Typically, myocardial perfusion defects are either due to obstructive atherosclerosis in epicardial coronary arteries or endothelial dysfunction. In diabetics, endothelial dysfunction is more common even without significant coronary artery obstruction, thus contributing significantly to myocardial perfusion abnormalities. Microalbuminuria and CAD share a common pathophysiology which is microangiopathy due to endothelial dysfunction. Microalbuminuria identifies a subset of patients at very high risk of developing complications i.e., proliferative retinopathy, renal insufficiency, and cardiovascular diseases [12, 13]. There is

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variable prevalence of SMI in asymptomatic diabetic patients across studies. Wackers et al., reported that 22% of patients had SMI [14]. Specifically, studies in Pakistan, including our own, have reported higher rates; in our study, 48% of patients exhibited SMI. This elevated prevalence can be attributed to referral bias, different diagnostic techniques, and a higher incidence of CAD in diabetic populations [15, 16]. Although, there are many studies assessing the significance of risk factors in anticipating silent myocardial ischemia in diabetic patients of Pakistan; however, none of these studies evaluated the role of microalbuminuria in predicting SMI using MPI [15, 16]. In Pakistan, the low socioeconomic status of patients is a big hurdle for diabetic patients to diagnose silent myocardial ischemia. However; the cost of MPS is low making it a suitable option for screening SMI in the diabetic population [17]. Our study suggests that diabetic patients with microalbuminuria should be screened for silent myocardial ischemia. Studies have shown a positive correlation of microalbuminuria with SMI; in our study, 58% of MAU-positive patients showed SMI [3, 18]. However, 25% of patients in our study had no MAU but had SMI. These patients had deranged HbA1c, a longer duration of diabetes, and were elderly. The reason for SMI might be atherosclerosis in coronary vessels. 42% of patients included in our study were positive for MAU but had no SMI. These patients had a shorter duration of diabetes, less mean age (51.1 years), and deranged HBA1c. Among the risk factors, we also assessed the role of HBA1c in predicting silent myocardial ischemia. In this study HBA1c greater than 7.3% was found to be significantly associated with CAD (61.3%), as compared to patients with HBA1C less than or equal to 7.3% (70%). Additionally, patients with microalbuminuria and SMI differed statistically significantly from patients with norm albuminuria and no SMI concerning HBA1c ($p<0.05$). Published studies support our data showing that HBA1C greater than 7% is associated with an increased incidence of CAD and increased ischemic burden [19]. Various risk factors among type II diabetics substantially increase the overall risk of CAD [20, 21]. Al-Humaidi G et al., published a study on asymptomatic diabetic patients with one or more risk factors for CAD and reported abnormal MPI in 37% of patients. Al-Humaidi G et al., further concluded that duration of diabetes, use of insulin, nephropathy, and neuropathy are significantly associated with abnormal myocardial scans [22]. Multiple risk factors assessment in our study such as hypertension, smoking, dyslipidemia, age, family history, and duration of diabetes were not predictors of silent myocardial ischemia. This could be because of the small sample size, referral bias, and study design. Some studies have not been able to correlate the number of risk factors with inducible ischemia on myocardial perfusion imaging among type II diabetics [23]. The difficulty may be because these studies did not consider the severity, duration, and effect of treatment of dyslipidemia and hypertension in patients with long-standing type II diabetes. In our study microalbuminuria seems to be an independent and strong predictor for CV disease. Our study established a positive relationship between microalbuminuria and silent myocardial ischemia. It is important to enhance the capability to sort out the patients who are at higher risk for cardiovascular events. Assessment of risk factor burden especially microalbuminuria might predict the risk of cardiovascular events in type II diabetic patients. There were certain limitations in our study such as small sample size, limited duration of study, and lack of follow-up of patients for assessment of cardiac events. Further studies are required with large sample size and extended duration of follow-up to evaluate the significance of microalbuminuria and SPECT MPS imaging in predicting myocardial ischemia among asymptomatic diabetic patients.

CONCLUSIONS

It was concluded that our study highlights that incorporating testing for microalbuminuria in asymptomatic diabetic patients can increase the predictive value of MPS SPECT imaging in detecting silent myocardial ischemia. This finding has important implications for treatment decision-making, as it may inform the need to progress to invasive tests. Our results underscore the value of non-invasive MPS imaging as a diagnostic tool for the early management of coronary artery disease in individuals with diabetes.

Authors Contribution

Conceptualization: NR, MIK
Methodology: TJ, WA, FG, MSA
Formal analysis: TJ, WA, FG, MSA, MBI
Writing review and editing: NR, MIK[1], MIK[2], MBI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

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